3724878 BIOSIS Number: 74024741

TRANSFER OF ALLERGIC ENCEPHALO MYELITIS WITH SPLEEN CELLS FROM DONORS SENSITIZED WITH MYELIN BASIC PROTEIN IN INCOMPLETE FREUNDS ADJUVANT

NAMIKAWA T; RICHERT J R; DRISCOLL B F; KIES M W; ALVORD E C JR
SECT. MYELIN CHEM., LAB. CEREBRAL METAB., NATL. INST. MENT. HEALTH, BETHESDA, MD. 20205.

J IMMUNOL 128 (2). 1982. 932-934. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

Myelin basic protein (BP) emulsified in incomplete Freund's adjuvant (BP/IFA) is relatively nonencephalitogenic in Lewis rats. Repeated injections of BP/IFA prevent subsequent induction of experimental allergic encephalomyelitis (EAE) by BP emulsified in complete Freund's adjuvant (BP/CFA). Spleen cells from rats injected repeatedly with BP/IFA transfer EAE after they are cultured with BP almost as effectively as BP/CFA spleen cells. Unlike the latter, BP/IFA spleen cells do not proliferate in response to BP in culture. BP/IFA spleen cells are unable to transer EAE after culture with concanavalin A (Con A), in contrast to BP/CFA spleen cells. Both populations of spleen cells undergo a strong proliferative response to Con A in culture. For BP/IFA cells, at least, a proliferative response to BP in vitro is not a prerequisite for enhanced transfer of EAE in Lewis rats.

Descriptors/Keywords: LEWIS RATS COMPLETE FREU

16/9/11 (Item 11 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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4502048 BIOSIS Number: 78075871

PARTICIPATION OF ENCEPHALITOGEN IN INCOMPLETE FREUNDS ADJUVANT IN THE INDUCTION OF EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN HARTLEY GUINEA-PIGS

LEBAR R; VINCENT C
U 23 INSERM, HOPITAL ST-ANTOINE, 184, RUE DE FG ST-ANTOINE, 75571 PARIS CEDEX 12, FR.

J NEUROIMMUNOL 6 (3). 1984. 187-196. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH

The addition of complete Freund's adjuvant (CFA) to encephalitogen is required for the induction of experimental allergic encephalomyelitis (EAE). Administration of encephalitogen in incomplete Freund's adjuvant (IFA) protects the animal from the development of EAE. Injection of homologous CNS tissue or myelin basic protein (BP) in IFA, before challenge with CNS tissue in CFA, accelerated the onset of the disease in Hartley guinea pigs. It also appeared to protect the animals, because 22% of the group did not develop EAE at all, and in those which did, the disease was not as lethal as in controls. To produce this accelerated form of EAE with encephalitogen in IFA required a time interval shorter than 9 days between the 1st injection and challenge and that the 1st injection and the challenge be done in the same site, which could be hind or front foot pads but not the nuchal area. Priming by encephalitogen in IFA occurred when this 2-step induction procedure was used. The experimental conditions may have bypassed suppressive mechanisms.

Descriptors/Keywords: COMPLETE FREUNDS ADJUVANT MYELIN BASIC PROTEIN

Concept Codes:
*20506 Nervous System-Pathology
*34502 Immunology and Immunochemistry-General; Methods

```
: EIU Market Research (File 768)
***New: TRADEMARKSCAN(R)-Ireland (File 676)
***New: Readers' Guide Abstracts Full Text (File 141)
***New: K-R Telecommunication Newsletters (File 696)
***New: CAB HEALTH (File 162)
                                        ***
***Reloaded: DIOGENES: FDA Regulatory Updates (File 158)
***Enhanced: CA SEARCH(R): Chemical Abstracts(R)
***Enhanced: SoftBase: Reviews, Companies, and Products (File 256)
***Enhanced: Latin American News (File 749)
***Removed: U.S. Political Science Documents (File 93)

                               ***FREE***
***File 162, CAB HEALTH--$15 free combined connect time/output
   during January--Free Alerts during January and February
***File 141, Readers' Guide Abstracts Fulltext--$20 free combined
   connect time/output during January--Free Alerts during January
   and February
***File 750, Middle East News----Free Alerts during January
***Files 428 and 429, Adis Newsletters--Free Alerts during January
***File 750, Middle East News--Free Alerts during January
***File 606, Africa News--Free Alerts during January
***File 607, ITAR/TASS News--Free Alerts during January
***File 618, Xinhua News--Free Alerts during January
***File 490, Tallahassee Democrat--Free Alerts during January
***File 489, (Fort Wayne) The News-Sentinel--Free Alerts during
   January
***See HELP FREE for details


Message from database supplier:
MEDLINE and CANCERLIT erroneously annotated certain articles
authored or co-authored by Dr. Bernard Fisher with the phrase
"scientific misconduct--data to be reanalyzed." All such
annotations have been removed or are being removed. We apologize
for any problems or concerns this may have caused. Users should
disregard those prior annotations.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
     >>>    Announcements last updated for 3jan97      <<<
* file 502 is now closed, please try again later*

File   1:ERIC  1966-1996/Nov
       (c) format only 1996 Knight-Ridder Info

      Set  Items  Description
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?b biotech,350,351

       08jan97 08:52:29 User219509 Session B38.1
            $0.18    0.006 Hrs File1
     $0.18  Estimated cost File1
     $0.18  Estimated cost this search
     $0.18  Estimated total session cost   0.006 Hrs.

SYSTEM:OS  - DIALOG OneSearch
  File   5:BIOSIS PREVIEWS(R)  1969-1996/Dec W4
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        (c) 1996 BIOSIS
*File   5: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 005 to see new prices."
  File  10:AGRICOLA  70-1996/Dec
        (c) format only 1996 Knight-Ridder Info
  File  12:IAC Industry Express (sm)  1995-1997/Jan 08
        (c) 1997 Info. Access Co.
*File  12: KWIC format pricing has changed effective 1/1/97.
See HELP RATES12 for new prices.
  File  42:PHARMACEUTICAL NEWS INDEX  1974-1997/Dec W5
        (c) 1997 UMI
*File 42: PD= and PY= will not work for dates earlier than 1988.
  File  43:Health News Daily  1990-1997/Jan 07
        (c) 1997 F-D-C reports Inc.
*File  43: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 043 to see new prices."
  File  50:CAB Abstracts  1972-1996/Nov
        (c) 1996 CAB International
*File  50: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 50 to see new prices.
  File  73:EMBASE  1974-1996/Iss 52
        (c) 1997 Elsevier Science B.V.
*File  73: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 073 to see new prices."
  File  76:Life Sciences Collection  1982-1996/Nov
        (c) 1996 Cambridge Sci Abs
*File  76: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 076 to see new prices."
  File  94:JICST-EPlus  1985-1997/Dec W2
        (c)1997 Japan Science and Tech Corp(JST)
*File  94: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 94 to see new prices.
  File 129:PHIND(Archival)  1980-1997/Jan W1
        (c) 1997 PJB Publications, Ltd.
  File 130:PHIND(Daily & Current)  1997/Jan 08
        (c) 1997 PJB Publications,Ltd.
  File 140:Unlisted Drugs 1984-1994/July  (c) 1995 Pharmaco Med. Documentation
Inc
*File 140: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 140 to see new prices."
  File 143:Biol. & Argic. Index  1983-1996/Nov
        (c) 1997 The HW Wilson Co
*File 143: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 143 to see new prices."
  File 144:Pascal  1973-1996/Dec
        (c) 1996 INIST/CNRS
*File 144: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 144 to see new prices.
  File 149:IAC(SM)Health&Wellness DB(SM)  1976-1997/Jan W1
        (c) 1997 Info Access Co
*File 149: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 149 to see new prices."
  File 155:MEDLINE(R)  1966-1997/Jan W4
        (c) format only 1996 Knight-Ridder Info
*File 155: "KWIC format pricing will change effective 1/1/97.See HELP
RATES 155 to see new prices." Medline updated delayed. See HELP DELAY 155.
  File 158:DIOGENES(R)  1982-1997/Jan W1
        (c) 1997 DIOGENES
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*File 158: File has been reloaded. Accession numbers have
changed. New KWIC pricing effective 1/1/97. See HELP RATES 158.
  File 172:EMBASE Alert 1996/Dec W5
       (c) 1996 Elservier Science B.V.
*File 172: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 172 to see new prices."
  File 187:F-D-C Reports 1987-1996/Dec W5
       (c) 1996 F-D-C Reports Inc.
*File 187: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 187 to see new prices."
  File 189:NDA Pipeline: New Drugs 1991-1996/Nov
       (c) 1996 F-D-C Reports Inc.
  File 211:IAC NewSearch(TM) 1996-1997/Jan 08
       (c) 1997 Info. Access Co.
*File 211: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 211 to see new prices.
  File 285:BioBusiness(R) 1985-1997/Jan W3
       (c) 1997 BIOSIS
*File 285: KWIC format pricing will change effective 1/1/97.
See HELP RATES 285 to see new prices.
  File 286:Biocommerce Abs.& Dir. 1981-1996/Dec B1
       (c) 1996 BioCommerce Data Ltd.
  File 315:ChemEng & Biotec Abs 1970-1996/Dec
       (c)1996 RoySocChm,DECHEMA,FizChemie
*File 315: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 315 to see new prices.
  File 357:Derwent Biotechnology Abs 1982-1997/Dec B3
       (c) 1997 Derwent Publ Ltd
*File 357: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 357 to see new prices."
  File 358:Current BioTech Abs 1983-1997/Jan
       Royal Soc Chem & DECHEMA
  File 376:Derwent Drug File 1964-1982
       (c) 1995 Derwent Info Ltd.
*File 376: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 376 to see new prices."
  File 377:Derwent Drug File 1983-1997/Jan W1
       (c) 1997 Derwent Info Ltd.
*File 377: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 377 to see new prices."
  File 428:Adis Newsletters(Current) 1997/Jan 08
       (c) 1997 Adis Intl. Ltd.
  File 429:Adis Newsletters(Archive) 1982-1996/Dec 11
       (c) 1997 Adis Intl. Ltd.
*File 429: Records between 1982 and 1993 will be available early 1997.
  File 434:Scisearch(R) Cited Ref Sci 1974-1996/Dec W4
       (c) 1997 Inst for Sci Info
*File 434: RANK now $0.02 per record as of 1/1/97. Changes to
Subject Categories effective Week 1, 1997. See HELP NEWS 434.
  File 446:IMSWorld Product Launches 1982-1996/Dec
       (c) 1996 IMSWorld Publ. Ltd.
*File 446: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 446 to see new prices."
  File 449:IMSWorld Company Profiles 1992-1996/Nov.
       (c) 1996 IMSworld Publ. Ltd.
*File 449: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 449 to see new prices."
  File 452:Drug Data Report 1992-1996/Dec

```
         (c) 1996 J.R. Prous S.A.
*File 452: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 452 to see new prices."
  File 455:Drug News & Perspectives  1992-1996/Dec
         (c) 1996 J.R. Prous S.A.
*File 455: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 455 to see new prices."
  File 456:NME Express  1992-1996/Nov B1
         (c) 1996 J.R. Prous, S.A.
*File 456: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 456 to see new prices."
  File 636:IAC Newsletter DB(TM)  1987-1997/Jan 08
         (c) 1997 Information Access Co.
  File 350:Derwent World Pat.  1963-1980/UD=9648
         (c) 1996 Derwent Info Ltd
  File 351:DERWENT WPI  1981-1996/UD=9701;UA=9649;UM=9641
         (c)1997 Derwent Info Ltd

      Set  Items  Description
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?s th2(w)response(w)inducing(w)adjuvant

Processed  20 of  39 files ...
Processing
Completed processing all files
           13154  TH2
         3346732  RESPONSE
          282275  INDUCING
          161081  ADJUVANT
      S1       0  TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
?e au=lehmann p


Ref   Items  Index-term
E1      597 *AU=LEHMANN P
E2       14  AU=LEHMANN P A
E3       11  AU=LEHMANN P A F
E4        1  AU=LEHMANN P E
E5       97  AU=LEHMANN P F
E6        1  AU=LEHMANN P H
E7        8  AU=LEHMANN P J
E8        7  AU=LEHMANN P M
E9        1  AU=LEHMANN P O
E10       1  AU=LEHMANN P POPPE W
E11       2  AU=LEHMANN P R
E12      57  AU=LEHMANN P V

          Enter P or PAGE for more
?e


Ref   Items  Index-term
E13     113  AU=LEHMANN P.
E14      10  AU=LEHMANN P.A.
E15       1  AU=LEHMANN P.A.F.
E16       1  AU=LEHMANN P.E.
E17      29  AU=LEHMANN P.F.
E18      21  AU=LEHMANN P.V.
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E19       43  AU=LEHMANN PA
E20        1  AU=LEHMANN PASCALE
E21        1  AU=LEHMANN PATRICK
E22        3  AU=LEHMANN PATRICK J
E23        3  AU=LEHMANN PE
E24       69  AU=LEHMANN PF

          Enter P or PAGE for more
?e


Ref    Items  Index-term
E25        4  AU=LEHMANN PH
E26        5  AU=LEHMANN PH.
E27        5  AU=LEHMANN PJ
E28        6  AU=LEHMANN PM
E29        1  AU=LEHMANN PO
E30       60  AU=LEHMANN PV
E31        1  AU=LEHMANN PW
E32     1022  AU=LEHMANN R
E33       13  AU=LEHMANN R E
E34        2  AU=LEHMANN R F
E35       62  AU=LEHMANN R G
E36        5  AU=LEHMANN R H

          Enter P or PAGE for more
?s e1-e31

>>>One or more prefixes are unsupported
>>>  or undefined in one or more files.
              597  AU=LEHMANN P
               14  AU=LEHMANN P A
               11  AU=LEHMANN P A F
                1  AU=LEHMANN P E
               97  AU=LEHMANN P F
                1  AU=LEHMANN P H
                8  AU=LEHMANN P J
                7  AU=LEHMANN P M
                1  AU=LEHMANN P O
                1  AU=LEHMANN P POPPE W
                2  AU=LEHMANN P R
               57  AU=LEHMANN P V
              113  AU=LEHMANN P.
               10  AU=LEHMANN P.A.
                1  AU=LEHMANN P.A.F.
                1  AU=LEHMANN P.E.
               29  AU=LEHMANN P.F.
               21  AU=LEHMANN P.V.
               43  AU=LEHMANN PA
                1  AU=LEHMANN PASCALE
                1  AU=LEHMANN PATRICK
                3  AU=LEHMANN PATRICK J
                3  AU=LEHMANN PE
               69  AU=LEHMANN PF
                4  AU=LEHMANN PH
                5  AU=LEHMANN PH.
                5  AU=LEHMANN PJ
                6  AU=LEHMANN PM
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                1  AU=LEHMANN PO
               60  AU=LEHMANN PV
                1  AU=LEHMANN PW
      S2     1174  E1-E31
?e


Ref    Items  Index-term
E37        1  AU=LEHMANN R K
E38        2  AU=LEHMANN R L
E39       35  AU=LEHMANN R P
E40       14  AU=LEHMANN R R
E41       22  AU=LEHMANN R W
E42      147  AU=LEHMANN R.
E43        1  AU=LEHMANN R.E.
E44        1  AU=LEHMANN R.F.
E45       13  AU=LEHMANN R.G.
E46        1  AU=LEHMANN R.H.
E47        7  AU=LEHMANN R.P.
E48        6  AU=LEHMANN R.R.

          Enter P or PAGE for more
?e au=lehmann, p


Ref    Items  Index-term
E1         0 *AU=LEHMANN, P
E2         3  AU=LEHMANN, P F
E3        15  AU=LEHMANN, P.
E4        36  AU=LEHMANN, P. F.
E5         2  AU=LEHMANN, P. V.
E6        24  AU=LEHMANN, P.F.
E7        17  AU=LEHMANN, P.V.
E8         1  AU=LEHMANN, PAUL F
E9         1  AU=LEHMANN, PAUL F.
E10        5  AU=LEHMANN, PAUL V
E11        3  AU=LEHMANN, PAUL V.
E12        1  AU=LEHMANN, PERCY

          Enter P or PAGE for more
?e


Ref    Items  Index-term
E13       18  AU=LEHMANN, PHYLLIS
E14        3  AU=LEHMANN, PHYLLIS E.
E15       13  AU=LEHMANN, R
E16        6  AU=LEHMANN, R P
E17      110  AU=LEHMANN, R.
E18       14  AU=LEHMANN, R. G
E19       22  AU=LEHMANN, R. G.
E20        3  AU=LEHMANN, R. H.
E21        1  AU=LEHMANN, R. P.
E22       16  AU=LEHMANN, R.G.
E23        2  AU=LEHMANN, R.P.
E24        1  AU=LEHMANN, R.R.

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?s e1-e14

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>>>  or undefined in one or more files.
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                3   AU=LEHMANN, P F
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               36   AU=LEHMANN, P. F.
                2   AU=LEHMANN, P. V.
               24   AU=LEHMANN, P.F.
               17   AU=LEHMANN, P.V.
                1   AU=LEHMANN, PAUL F
                1   AU=LEHMANN, PAUL F.
                5   AU=LEHMANN, PAUL V
                3   AU=LEHMANN, PAUL V.
                1   AU=LEHMANN, PERCY
               18   AU=LEHMANN, PHYLLIS
                3   AU=LEHMANN, PHYLLIS E.
      S3      129   E1-E14
?ds


Set      Items   Description
S1           0   TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
S2        1174   E1-E31
S3         129   E1-E14
?s s2 or s3

            1174   S2
             129   S3
      S4    1303   S2 OR S3
?s s4 and th2

            1303   S4
           13154   TH2
      S5      15   S4 AND TH2
?rd

>>>Duplicate detection is not supported for File 42.
>>>Duplicate detection is not supported for File 43.
>>>Duplicate detection is not supported for File 94.
>>>Duplicate detection is not supported for File 129.
>>>Duplicate detection is not supported for File 130.
>>>Duplicate detection is not supported for File 140.
>>>Duplicate detection is not supported for File 187.
>>>Duplicate detection is not supported for File 286.
>>>Duplicate detection is not supported for File 428.
>>>Duplicate detection is not supported for File 429.
>>>Duplicate detection is not supported for File 446.
>>>Duplicate detection is not supported for File 449.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 455.
>>>Duplicate detection is not supported for File 456.
>>>Duplicate detection is not supported for File 350.
>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
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S6 8 RD (unique items)
?t s6/3/1-8

6/3/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13006471 BIOSIS Number: 99006471
Nasal administration of glutamate decarboxylase (GAD65) peptides induces Th2 responses and prevents murine insulin-dependent diabetes
Tian J; Atkinson M A; Clare-Salzler M; Herschenfeld A; Forsthuber T; Lehmann P V; Kaufman D L
Dep. Molecular Med. Pharmacol., Univ. California, Los Angeles, CA 90095-1735, USA
Journal of Experimental Medicine 183 (4). 1996. 1561-1567.
Full Journal Title: Journal of Experimental Medicine
ISSN: 0022-1007
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 001 Ref. 006471

6/3/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

11795914 BIOSIS Number: 98395914
TH1 and TH2 activity in mice resistant and susceptible to EAE
Johnsen A K; Forsthuber T; Trezza R; Lehmann P V
Sch. Med., Dep. Pathos. Case Western Reserve Univ., Cleveland, OH, USA
0 (0). 1995. 170.
Full Journal Title: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY. The 9th International Congress of Immunology; Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies, San Francisco, California, USA, July 23-29, 1995. ix+742p. 9th International Congress of Immunology: San Francisco, California, USA.
ISSN: *********
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 009 Ref. 158317

6/3/3 (Item 1 from file: 143)
DIALOG(R)File 143:Biol. & Argic. Index
(c) 1997 The HW Wilson Co. All rts. reserv.

0620205 H.W. WILSON RECORD NUMBER: BBAI96017464
Induction of TH1 and TH2 immunity in neonatal mice
Forsthuber, Thomas
Yip, Hualin C; Lehmann, Paul V
Science v. 271 (Mar. 22 '96) p. 1728-30
DOCUMENT TYPE: Feature Article ISSN: 0036-8075

6/3/4 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

12520901 PASCAL No.: 96-0194925
Induction of T SUB H 1 and T SUB H 2 immunity in neonatal mice
FORSTHUBER T; YIP H C; LEHMANN P V
Department of Pathology, Biomedical Research Building, Case Western Reserve University, Cleveland OH, 44106-4943, United States
Journal: Science : (Washington, DC), 1996, 271 (5256) 1728-1730
Language: English

6/3/5 (Item 1 from file: 172)
DIALOG(R)File 172:EMBASE Alert
(c) 1996 Elservier Science B.V. All rts. reserv.

00275659 EMBASE No: 96366589
Modulating autoimmune responses to GAD inhibits disease progression and prolongs islet graft survival in diabetes-prone mice
Tian J.; Clare-Salzler M.; Herschenfeld A.; Middleton B.; Newman D.; Mueller R.; Arita S.; Evans C.; Atkinson M.A.; Mullen Y.; Sarvetnick N.; Tobin A.J.; Lehmann P.V.; Kaufman D.L.
Dept. of Mol./Med. Pharmacology, University of California, Postal Code 90095-1735, Los Angeles, CA 90095 USA
Nature Medicine (USA) , 1996
Vol/Iss/Pg: 2/12 (1348-1353) CODEN: NAMEF ISSN: 1078-8956
LANGUAGES: English SUMMARY LANGUAGES: English

6/3/6 (Item 1 from file: 377)
DIALOG(R)File 377:Derwent Drug File
(c) 1997 Derwent Info Ltd. All rts. reserv.

00715977 DERWENT ACCESSION NUMBER: 96-44603
Topical FK506: suppression of Th1 and Th2 cytokine induction in lymph node cells in vivo.
Homey B; Assmann T; Vohr H W; Lauerma A I; Ruzicka T; Lehmann P;
Schuppe H C
Univ.Dusseldorf Univ.Helsinki Bayer (Dusseldorf; Wuppertal, Ger.;
Helsinki, Fin.)
J.Invest.Dermatol. 107, No. 3, 476, 1996

6/3/7 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15118928 Genuine Article#: VK074 No. References: 0
Title: INDUCTION OF A RENAL TUBULAR ANTIGEN (RTA)-SPECIFIC TH2 RESPONSE PREVENTS MURINE ANTI-TUBULAR BASEMENT-MEMBRANE (ALPHA-TBM) DISEASE
Author(s): HEEGER P; FORSTHUBER T; BIEKERT E; LEHMANN PV
Corporate Source: CASE WESTERN RESERVE UNIV/CLEVELAND//OH/44106; VET ADM MED CTR/CLEVELAND//OH/44106
Journal: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, 1996, V7, N9 (SEP), PA2278
ISSN: 1046-6673
Language: ENGLISH Document Type: MEETING ABSTRACT

6/3/8 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci

(c) 1997 Inst for Sci Info. All rts. reserv.

14607682 Genuine Article#: UB151 No. References: 35
Title: INDUCTION OF T(H)1 AND T(H)2 IMMUNITY IN NEONATAL MICE
Author(s): FORSTHUBER T; YIP HC; LEHMANN PV
Corporate Source: CASE WESTERN RESERVE UNIV,DEPT PATHOL,BIOMED RES
BLDG/CLEVELAND//OH/44106; CASE WESTERN RESERVE UNIV,DEPT
PATHOL/CLEVELAND//OH/44106
Journal: SCIENCE, 1996, V271, N5256 (MAR 22), P1728-1730
ISSN: 0036-8075
Language: ENGLISH Document Type: ARTICLE (Abstract Available)
?t s6/9/1-6

6/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13006471 BIOSIS Number: 99006471
Nasal administration of glutamate decarboxylase (GAD65) peptides induces Th2 responses and prevents murine insulin-dependent diabetes
Tian J; Atkinson M A; Clare-Salzler M; Herschenfeld A; Forsthuber T; Lehmann P V; Kaufman D L
Dep. Molecular Med. Pharmacol., Univ. California, Los Angeles, CA 90095-1735, USA
Journal of Experimental Medicine 183 (4). 1996. 1561-1567.
Full Journal Title: Journal of Experimental Medicine
ISSN: 0022-1007
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 001 Ref. 006471
We previously demonstrated that a spontaneous Th1 response against glutamate decarboxylase (GAD65) arises in NOD mice at four weeks in age and subsequently T cell autoimmunity spreads both intramolecularly and intermolecularly. Induction of passive tolerance to GAD65, through the inactivation of reactive T cells before the onset of autoimmunity, prevented determinant spreading and the development of insulin-dependent diabetes mellitus (IDDM). Here, we examined whether an alternative strategy, designed to induce active tolerance via the engagement of Th2 immune responses to GAD65, before the spontaneous onset of autoimmunity, could inhibit the cascade of Th1 responses that lead to IDDM. We observed that a single intranasal administration of GAD65 peptides to 2-3-wk-old NOD mice induced high levels of IgG-1 antibodies to GAD65. GAD65 peptide treated mice displayed greatly reduced IFN-gamma responses and increased IL-5 responses to GAD65, confirming the diversion of the spontaneous GAD65 Th1 response toward a Th2 phenotype. Consistent with the induction of an active tolerance mechanism, splenic CD4+ (but not CD8+) T cells from GAD65 peptide-treated mice, inhibited the adoptive transfer of IDDM to NOD-scid/scid mice. This active mechanism not only inhibited the development of proliferative T cell responses to GAD65, it also limited the expansion of autoreactive T cell responses to other beta cell antigens (i.e., determinant spreading). Finally, GAD65 peptide treatment reduced insulitis and long-term IDDM incidence. Collectively, these data suggest that the nasal administration of GAD65 peptides induces a Th2 cell response that inhibits the spontaneous development of autoreactive Th1 responses and the progression of beta cell autoimmunity in NOD mice.
Descriptors/Keywords: RESEARCH ARTICLE; NON-OBESE DIABETIC MOUSE; INSULIN-DEPENDENT DIABETES MELLITUS; T-CELL AUTOIMMUNITY; AUTOREACTIVE TH1 RESPONSE; BETA-CELL AUTOIMMUNITY PROGRESSION

Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10054 Biochemical Methods-Proteins, Peptides and Amino Acids
*10058 Biochemical Methods-Carbohydrates
*10806 Enzymes-Chemical and Physical
*10808 Enzymes-Physiological Studies
*13004 Metabolism-Carbohydrates
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13020 Metabolism-Metabolic Disorders
*15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph Studies
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*16001 Respiratory System-General; Methods
*17008 Endocrine System-Pancreas
*22100 Routes of Immunization, Infection and Therapy
*25508 Developmental Biology-Embryology-Morphogenesis, General
*34502 Immunology and Immunochemistry-General; Methods
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10068 Biochemical Studies-Carbohydrates
10504 Biophysics-General Biophysical Techniques

Biosystematic Codes:
86375 Muridae

Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

6/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11795914 BIOSIS Number: 98395914
TH1 and TH2 activity in mice resistant and susceptible to EAE
Johnsen A K; Forsthuber T; Trezza R; Lehmann P V
Sch. Med., Dep. Pathos. Case Western Reserve Univ., Cleveland, OH, USA
0 (0). 1995. 170.
Full Journal Title: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY. The 9th International Congress of Immunology; Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies, San Francisco, California, USA, July 23-29, 1995. ix+742p. 9th International Congress of Immunology: San Francisco, California, USA.
ISSN: *********
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 047 Iss. 009 Ref. 158317
Descriptors/Keywords: MEETING ABSTRACT; T-HELPER 1 CELLS; T-HELPER 2 CELLS; EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS; AUTOIMMUNE DISEASE GENETICS; ELISA SPOT ASSAY

Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10052 Biochemical Methods-Nucleic Acids, Purines and Pyrimidines
*10062 Biochemical Studies-Nucleic Acids, Purines and Pyrimidines

*10064 Biochemical Studies-Proteins, Peptides and Amino Acids
*10506 Biophysics-Molecular Properties and Macromolecules
*12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*20502 Nervous System-Anatomy
*20506 Nervous System-Pathology
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
10054 Biochemical Methods-Proteins, Peptides and Amino Acids
10504 Biophysics-General Biophysical Techniques
10804 Enzymes-Methods

Biosystematic Codes:
86375 Muridae

Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

6/9/3 (Item 1 from file: 143)
DIALOG(R)File 143:Biol. & Argic. Index
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0620205 H.W. WILSON RECORD NUMBER: BBAI96017464
Induction of TH1 and TH2 immunity in neonatal mice
Forsthuber, Thomas
Yip, Hualin C; Lehmann, Paul V
Science v. 271 (Mar. 22 '96) p. 1728-30
DOCUMENT TYPE: Feature Article ISSN: 0036-8075 LANGUAGE: English
RECORD STATUS: Corrected or revised record
In: Science v. 271 (Mar. 22 '96) p. 1728-30; Discussion. v272 p1405-8 Je 7 '96.

DESCRIPTORS: Helper cells; Immunity

6/9/4 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

12520901 PASCAL No.: 96-0194925
Induction of T SUB H 1 and T SUB H 2 immunity in neonatal mice
FORSTHUBER T; YIP H C; LEHMANN P V
Department of Pathology, Biomedical Research Building, Case Western Reserve University, Cleveland OH, 44106-4943, United States
Journal: Science : (Washington, DC), 1996, 271 (5256) 1728-1730
ISSN: 0036-8075 CODEN: SCIEAS Availability: INIST-6040; 354000044735840220
Document Type: P (Serial); C (Book review) ; A (Analytic)
Country of Publication: United States
Note: 1/2 p. ref. et notes
Language: English
The neonatal period has been thought of as a window in ontogeny, during which the developing immune system is particularly susceptible to

tolerization. In the present study, the classic system for induction of neonatal tolerance to protein antigens was reexamined in mice. The presumably tolerogenic protocol was found to trigger a vigorous T helper cell type 2 (T SUB H 2) immune response. Thus, neonatal "tolerization" induces immune deviation, not tolerance in the immunological sense. Neonates are not immune privileged but generate T SUB H 2 or T SUB H 1 responses, depending on the mode of immunization.
English Descriptors: Helper cell; Mouse; Newborn animal; Cellular immunity; T-Lymphocyte; Immune tolerance
Broad Descriptors: Rodentia; Mammalia; Vertebrata; Immune response; Rodentia; Mammalia; Vertebrata; Reponse immune; Rodentia; Mammalia; Vertebrata; Respuesta inmune

French Descriptors: Cellule helper; Souris; Animal nouveau ne; Immunite cellulaire; Lymphocyte T; Tolerance immune; Lymphocyte Th1; Lymphocyte Th2

Classification Codes: 002A06C07

6/9/5 (Item 1 from file: 172)
DIALOG(R)File 172:EMBASE Alert
(c) 1996 Elservier Science B.V. All rts. reserv.

00275659 EMBASE No: 96366589
Modulating autoimmune responses to GAD inhibits disease progression and prolongs islet graft survival in diabetes-prone mice
Tian J.; Clare-Salzler M.; Herschenfeld A.; Middleton B.; Newman D.; Mueller R.; Arita S.; Evans C.; Atkinson M.A.; Mullen Y.; Sarvetnick N.; Tobin A.J.; Lehmann P.V.; Kaufman D.L.
Dept. of Mol./Med. Pharmacology, University of California, Postal Code 90095-1735, Los Angeles, CA 90095 USA
Nature Medicine (USA) , 1996
Vol/Iss/Pg: 2/12 (1348-1353) CODEN: NAMEF ISSN: 1078-8956
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English

In nonobese diabetic (NOD) mice, beta-cell reactive T-helper type 1 (Th1) responses develop spontaneously and gradually spread, creating a cascade of responses that ultimately destroys the beta-cells. The diversity of the autoreactive T-cell repertoire creates a major obstacle to the development of therapeutics. We show that even in the presence of established Th1 responses, it is possible to induce autoantigen-specific anti-inflammatory Th2 responses. Immune deviation of T-cell responses to the beta-cell autoantigen glutamate decarboxylase (GAD65), induced an active form of self-tolerance that was associated with an inhibition of disease progression in prediabetic mice and prolonged survival of syngeneic islet grafts in diabetic NOD mice. Thus, modulation of autoantigen-specific Th1/Th2 balances may provide a minimally invasive means of downregulating established pathogenic autoimmune responses.

6/9/6 (Item 1 from file: 377)
DIALOG(R)File 377:Derwent Drug File
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00715977 DERWENT ACCESSION NUMBER: 96-44603

Topical FK506: suppression of Th1 and Th2 cytokine induction in lymph node cells in vivo.
Homey B; Assmann T; Vohr H W; Lauerma A I; Ruzicka T; Lehmann P; Schuppe H C
Univ.Dusseldorf Univ.Helsinki Bayer (Dusseldorf; Wuppertal, Ger.; Helsinki, Fin.)
J.Invest.Dermatol. 107, No. 3, 476, 1996
CODEN: JIDEAE ISSN: 0022-202X LANGUAGE: English RECORD TYPE: Abstract

REPRINT ADDRESS: Department of Dermatology, University of Duesseldorf, Germany.

ABSTRACT:
Immunosuppressive effects of topical tacrolimus (FK-506) on cytokine expression in lymph node cells were investigated in mice treated with the contact sensitizer, topical oxazolone. Topical FK-506 suppressed both Th1 cytokine (IFN-gamma, IL-2) and Th2 cytokine (IL-4) mRNA expression in lymph node cells. The results give insights into the mechanisms of action of topical FK-506 in the treatment of inflammatory skin diseases and suggest that topical FK-506 may act by modulation of Th1/Th2 dysbalance in different stages of atopic dermatitis. (conference abstract).
LINK TERMS:
01; TACROLIMUS --PH; DERMATITIS --OC; HYPERSENSITIVITY --OC; CONTACT --OC ; DERMATOLOGY --OC; ALLERGY --OC; OXAZOLONE --RC; FK-506 --RN; MOUSE --FT ; IN-VIVO --FT; IMMUNOSUPPRESSIVE --FT; INTERFERON-GAMMA --FT; INTERLEUKIN-2 --FT; INTERLEUKIN-4 --FT; MESSENGER --FT; RNA --FT; EXPRESSION --FT; DERMATOLOGICAL --FT; MODE-OF-ACT. --FT; LAB.ANIMAL --FT; IMMUNOSUPPRESSIVES --FT; PH --FT;*01*; 104987-11-3

CAS(R) REGISTRY NUMBERS: *01* 104987-11-3
SECTION HEADINGS: Immunological (20); Dermatological (36); Biol. Response Modifiers (50)
THEMATIC GROUPS: P (Pharmacology)
?t s6/9/7,8

6/9/7 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15118928 Genuine Article#: VK074 Number of References: 0
Title: INDUCTION OF A RENAL TUBULAR ANTIGEN (RTA)-SPECIFIC TH2 RESPONSE PREVENTS MURINE ANTI-TUBULAR BASEMENT-MEMBRANE (ALPHA-TBM) DISEASE
Author(s): HEEGER P; FORSTHUBER T; BIEKERT E; LEHMANN PV
Corporate Source: CASE WESTERN RESERVE UNIV/CLEVELAND//OH/44106; VET ADM MED CTR/CLEVELAND//OH/44106
Journal: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, 1996, V7, N9 (SEP) , PA2278
ISSN: 1046-6673
Language: ENGLISH Document Type: MEETING ABSTRACT
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences; CC CLIN--Current Contents, Clinical Medicine
Journal Subject Category: UROLOGY & NEPHROLOGY

6/9/8 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci

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14607682 Genuine Article#: UB151 Number of References: 35
Title: INDUCTION OF T(H)1 AND T(H)2 IMMUNITY IN NEONATAL MICE
Author(s): FORSTHUBER T; YIP HC; LEHMANN PV
Corporate Source: CASE WESTERN RESERVE UNIV,DEPT PATHOL,BIOMED RES BLDG/CLEVELAND//OH/44106; CASE WESTERN RESERVE UNIV,DEPT PATHOL/CLEVELAND//OH/44106
Journal: SCIENCE, 1996, V271, N5256 (MAR 22), P1728-1730
ISSN: 0036-8075
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC PHYS--Current Contents, Physical, Chemical & Earth Sciences; CC LIFE--Current Contents, Life Sciences; CC AGRI--Current Contents, Agriculture, Biology & Environmental Sciences
Journal Subject Category: MULTIDISCIPLINARY SCIENCES
Abstract: The neonatal period has been thought of as a window in ontogeny, during which the developing immune system is particularly susceptible to tolerization. In the present study, the classic system for induction of neonatal tolerance to protein antigens was reexamined in mice. The presumably tolerogenic protocol was found to trigger a vigorous T helper cell type 2 (T(H)2) immune response. Thus, neonatal ''tolerization'' induces immune deviation, not tolerance in the immunological sense. Neonates are not immune privileged but generate T(H)2 or T(H)1 responses, depending on the mode of immunization.
Identifiers--KeyWords Plus: EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS; MEMORY T-CELLS; EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS; MYELIN BASIC-PROTEIN; TOLERANCE INDUCTION; MIGRATION PATHWAYS; DETERMINANT; PEPTIDE; SPLEEN
Research Fronts: 94-0428 002 (MEMORY CD4(+) T-CELL ADHESION; MULTIPLE SUBSETS; DIFFERENTIAL EXPRESSION; CD45RA(+) PERIPHERAL-BLOOD LYMPHOCYTES)
94-0549 002 (CLINICAL ISLET TRANSPLANTATION; XENOREACTIVE HUMAN NATURAL ANTIBODIES; DISCORDANT XENOGRAFTS; PORCINE PANCREAS)
94-1498 001 (CYTOKINES IN LEISHMANIASIS; TH2 CELLS; IMMUNOLOGICAL ASPECTS OF ASTHMA; HUMAN ALLERGIC RESPONSE)
Cited References:
ABRAMOWICZ D, 1990, V20, P1647, EUR J IMMUNOL
ASHERSON GL, 1967, V23, P24, BR MED B
ASHERSON GL, 1965, V9, P205, IMMUNOLOGY
BERNARD CCA, 1977, V29, P100, CLINICAL EXPT IMMUNO
BILLINGHAM RE, 1953, V172, P603, NATURE
BRADLEY LM, 1992, V148, P324, J IMMUNOL
BURNET FM, 1949, P102, PRODUCTION ANTIBODIE
CHEN H, 1995, V60, P1182, TRANSPLANTATION
CHEN N, 1995, V60, P1187, TRANSPLANTATION
CLAYTON JP, 1989, V169, P1681, J EXP MED
DORSCH S, 1975, V258, P233, NATURE
EINSTEIN ER, 1968, V5, P567, IMMUNOCHEMISTRY
FALK GA, 1969, V103, P1248, J IMMUNOL
FORSTHUBER T, UNPUB
GAMMON G, 1986, V319, P413, NATURE
GAMMON GM, 1986, V164, P667, J EXP MED
HEINZEL FP, 1989, V169, P59, J EXP MED
JUNG TM, 1988, V141, P4110, J IMMUNOL
KEARNEY ER, 1994, V1, P327, IMMUNITY
LEHMANN PV, 1992, V358, P155, NATURE
MACKAY CR, 1992, V22, P887, EUR J IMMUNOL

MACKAY CR, 1991, V12, P189, IMMUNOL TODAY
MACKAY CR, 1990, V171, P801, J EXP MED
MOSMANN TR, 1989, V7, P145, ANNU REV IMMUNOL
OWEN RD, 1946, V37, P291, J HERED
OWEN RD, 1945, V102, P400, SCIENCE
PABST R, 1989, V108, P83, IMMUNOL REV
PABST R, 1988, V9, P43, IMMUNOL TODAY
PATERSON PY, 1958, V73, P811, ANN NY ACAD SCI
POWELL TJ, 1990, V144, P854, J IMMUNOL
QIN Y, 1989, V19, P373, EUR J IMMUNOL
RIEGER M, 1977, V4, P61, J IMMUNOGENET
SWIERKOSZ JE, 1974, V33, P814, FED PROC
SWIERKOSZ JE, 1975, V115, P631, J IMMUNOL
WELCH AM, 1976, V6, P910, EUR J IMMUNOL


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?ds


Set      Items   Description
S1           0   TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
S2        1174   E1-E31
S3         129   E1-E14
S4        1303   S2 OR S3
S5          15   S4 AND TH2
S6           8   RD (unique items)
?s th2 and autoimmun

            13154   TH2
              376   AUTOIMMUN
      S7       23   TH2 AND AUTOIMMUN
?s th2 and autoimmun?

            13154   TH2
           271791   AUTOIMMUN?
      S8     1403   TH2 AND AUTOIMMUN?
?s s8 and adjuvant?

             1403   S8
           184545   ADJUVANT?
      S9      120   S8 AND ADJUVANT?
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>>>      $0.06  Estimated cost File12
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>>>      $3.12  Estimated cost File144
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>>>             $0.30    0.010 Hrs File155
>>>      $0.30  Estimated cost File155
>>>             $0.18    0.002 Hrs File158
>>>      $0.18  Estimated cost File158
>>>             $0.36    0.004 Hrs File172
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>>>                $2.25  1 Type(s) in Format  9
>>>             $4.50  2 Types
>>>      $4.86  Estimated cost File172
>>>             $0.24    0.002 Hrs File187
>>>      $0.24  Estimated cost File187
>>>             $0.15    0.001 Hrs File189
>>>      $0.15  Estimated cost File189
>>>             $0.15    0.002 Hrs File211
>>>      $0.15  Estimated cost File211
>>>             $0.23    0.003 Hrs File285
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>>>      $0.12  Estimated cost File358
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>>>      $0.65  Estimated cost File351
>>>             OneSearch, 39 files,  0.150 Hrs FileOS
>>>     $35.84  Estimated cost this search
>>>     $36.02  Estimated total session cost   0.156 Hrs.
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* file 502 is now closed, please try again later*

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*File   5: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 005 to see new prices."
  File  10:AGRICOLA  70-1996/Dec
         (c) format only 1996 Knight-Ridder Info
  File  12:IAC Industry Express (sm)  1995-1997/Jan 08
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See HELP RATES12 for new prices.
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*File 42: PD= and PY= will not work for dates earlier than 1988.
  File  43:Health News Daily  1990-1997/Jan 07
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*File  43: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 043 to see new prices."
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         (c) 1996 CAB International
*File  50: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 50 to see new prices.
  File  73:EMBASE  1974-1996/Iss 52
         (c) 1997 Elsevier Science B.V.
*File  73: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 073 to see new prices."
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See HELP RATES 076 to see new prices."
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*File  94: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 94 to see new prices.
  File 129:PHIND(Archival)  1980-1997/Jan W1
         (c) 1997 PJB Publications, Ltd.
  File 130:PHIND(Daily & Current)  1997/Jan 08
         (c) 1997 PJB Publications,Ltd.
  File 140:Unlisted Drugs 1984-1994/July  (c) 1995 Pharmaco Med. Documentation
Inc
*File 140: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 140 to see new prices."
  File 143:Biol. & Argic. Index  1983-1996/Nov
         (c) 1997 The HW Wilson Co
*File 143: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 143 to see new prices."
  File 144:Pascal  1973-1996/Dec
         (c) 1996 INIST/CNRS
*File 144: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 144 to see new prices.
  File 149:IAC(SM)Health&Wellness DB(SM)  1976-1997/Jan W1
         (c) 1997 Info Access Co
*File 149: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 149 to see new prices."
  File 155:MEDLINE(R)  1966-1997/Jan W4
         (c) format only 1996 Knight-Ridder Info
ds
*File 155: "KWIC format pricing will change effective 1/1/97.See HELP
RATES 155 to see new prices." Medline updated delayed. See HELP DELAY 155.
  File 158:DIOGENES(R)  1982-1997/Jan W1
         (c) 1997 DIOGENES
*File 158: File has been reloaded. Accession numbers have
changed. New KWIC pricing effective 1/1/97.  See HELP RATES 158.
  File 172:EMBASE Alert  1996/Dec W5
         (c) 1996 Elservier Science B.V.
*File 172:  "KWIC format pricing will change effective 1/1/97.
See HELP RATES 172 to see new prices."
  File 187:F-D-C Reports  1987-1996/Dec W5
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(c) 1996 F-D-C Reports Inc.
*File 187: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 187 to see new prices."
File 189:NDA Pipeline: New Drugs 1991-1996/Nov
(c) 1996 F-D-C Reports Inc.
File 211:IAC NewSearch(TM) 1996-1997/Jan 08
(c) 1997 Info. Access Co.
*File 211: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 211 to see new prices.
File 285:BioBusiness(R) 1985-1997/Jan W3
(c) 1997 BIOSIS
*File 285: KWIC format pricing will change effective 1/1/97.
See HELP RATES 285 to see new prices.
File 286:Biocommerce Abs.& Dir. 1981-1996/Dec B1
(c) 1996 BioCommerce Data Ltd.
File 315:ChemEng & Biotec Abs 1970-1996/Dec
(c)1996 RoySocChm,DECHEMA,FizChemie
*File 315: KWIC format pricing has changed effective 1/1/97.
See HELP RATES 315 to see new prices.
File 357:Derwent Biotechnology Abs 1982-1997/Dec B3
(c) 1997 Derwent Publ Ltd
*File 357: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 357 to see new prices."
File 358:Current BioTech Abs 1983-1997/Jan
Royal Soc Chem & DECHEMA
File 376:Derwent Drug File 1964-1982
(c) 1995 Derwent Info Ltd.
*File 376: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 376 to see new prices."
File 377:Derwent Drug File 1983-1997/Jan W1
(c) 1997 Derwent Info Ltd.
*File 377: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 377 to see new prices."
File 428:Adis Newsletters(Current) 1997/Jan 08
(c) 1997 Adis Intl. Ltd.
File 429:Adis Newsletters(Archive) 1982-1996/Dec 11
(c) 1997 Adis Intl. Ltd.
*File 429: Records between 1982 and 1993 will be available early 1997.
File 434:Scisearch(R) Cited Ref Sci 1974-1996/Dec W4
(c) 1997 Inst for Sci Info
*File 434: RANK now $0.02 per record as of 1/1/97. Changes to
Subject Categories effective Week 1, 1997. See HELP NEWS 434.
File 446:IMSWorld Product Launches 1982-1996/Dec
(c) 1996 IMSWorld Publ. Ltd.
*File 446: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 446 to see new prices."
File 449:IMSWorld Company Profiles 1992-1996/Nov.
(c) 1996 IMSworld Publ. Ltd.
*File 449: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 449 to see new prices."
File 452:Drug Data Report 1992-1996/Dec
(c) 1996 J.R. Prous S.A.
*File 452: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 452 to see new prices."
File 455:Drug News & Perspectives 1992-1996/Dec
(c) 1996 J.R. Prous S.A.
*File 455: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 455 to see new prices."

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  File 456:NME Express  1992-1996/Nov B1
         (c) 1996 J.R. Prous, S.A.
*File 456: "KWIC format pricing will change effective 1/1/97.
See HELP RATES 456 to see new prices."
  File 636:IAC Newsletter DB(TM)  1987-1997/Jan 08
         (c) 1997 Information Access Co.
  File 350:Derwent World Pat.  1963-1980/UD=9648
         (c) 1996 Derwent Info Ltd
  File 351:DERWENT WPI  1981-1996/UD=9701;UA=9649;UM=9641
         (c)1997 Derwent Info Ltd

      Set  Items  Description
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?

Set      Items   Description
S1           0   TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
S2        1174   E1-E31
S3         129   E1-E14
S4        1303   S2 OR S3
S5          15   S4 AND TH2
S6           8   RD (unique items)
S7          23   TH2 AND AUTOIMMUN
S8        1403   TH2 AND AUTOIMMUN?
S9         120   S8 AND ADJUVANT?
?s s9


     S10     120  S9
?
?rd

>>>Duplicate detection is not supported for File 42.
>>>Duplicate detection is not supported for File 43.
>>>Duplicate detection is not supported for File 94.
>>>Duplicate detection is not supported for File 129.
>>>Duplicate detection is not supported for File 130.
>>>Duplicate detection is not supported for File 140.
>>>Duplicate detection is not supported for File 187.
>>>Duplicate detection is not supported for File 286.
>>>Duplicate detection is not supported for File 428.
>>>Duplicate detection is not supported for File 429.
>>>Duplicate detection is not supported for File 446.
>>>Duplicate detection is not supported for File 449.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 455.
>>>Duplicate detection is not supported for File 456.
>>>Duplicate detection is not supported for File 350.
>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
     S11      78  RD (unique items)
?s s11 not s6

              78  S11
```

8 S6
S12 78 S11 NOT S6
?t s12/3/1-78

12/3/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13248714 BIOSIS Number: 99248714
Both CD4+ and CD8+ T-cells in syngeneic islet grafts in NOD mice produce interferon-gamma during beta-cell destruction
Suarez-Pinzon W; Rajotte R V; Mosmann T R; Rabinovitch A
430 Heritage Med. Res. Centre, Univ. Alberta, Edmonton, AB T6G 2S2, Canada
Diabetes 45 (10). 1996. 1350-1357.
Full Journal Title: Diabetes
ISSN: 0012-1797
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 011 Ref. 164344

12/3/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13152495 BIOSIS Number: 99152495
Immunization of non-obese diabetic (NOD) mice with glutamic acid decarboxylase-derived peptide 524-543 reduces cyclophosphamide-accelerated diabetes
Sai P; Rivereau A S; Granier C; Haertle T; Martignat L
Immuno-Endocrinol., ENVN, Route de Gachet, CP 3013, 44087 Nantes Cedex 03, France
Clinical and Experimental Immunology 105 (2). 1996. 330-337.
Full Journal Title: Clinical and Experimental Immunology
ISSN: 0009-9104
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 007 Ref. 100626

12/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13103589 BIOSIS Number: 99103589
Relationship between Th1-Thy2 cytokine patterns and the arthritogenic response in collagen-induced arthritis
Mauri C; Williams R O; Walmsley M; Feldmann M
Inst. Rheumatol., 1 Lurgan Ave., Hammersmith, London W6 8LW, UK
European Journal of Immunology 26 (7). 1996. 1511-1518.
Full Journal Title: European Journal of Immunology
ISSN: 0014-2980
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 005 Ref. 069038

12/3/4 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

(c) 1996 BIOSIS. All rts. reserv.

13088216 BIOSIS Number: 99088216
Antigen based therapies to prevent diabetes in NOD mice
Ramiya V K; Shang X-Z; Pharis P G; Wasserfall C H; Stabler T V; Muir A B; Schatz D A; Maclaren N K
Dep. Pathol. Lab. Med., PO Box 100275, Univ. Fla., Gainesville, FL 32610-0275, USA
Journal of Autoimmunity 9 (3). 1996. 349-356.
Full Journal Title: Journal of Autoimmunity
ISSN: 0896-8411
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 004 Ref. 053665

12/3/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13039712 BIOSIS Number: 99039712
Heat shock proteins and experimental autoimmune encephalomyelitis (EAE): I. Immunization with a peptide of the myelin protein 2',3' cyclic nucleotide 3' phosphodiesterase that is cross-reactive with a heat shock protein alters the course of EAE
Birnbaum G; Kotilinek L; Schlievert P; Clark H B; Trotter J; Horvath E; Gao E; Cox M; Braun P E
Dep. Neurol., Univ. Minnesota, Box 295, UMHC, Minneapolis, MN 55455, USA
Journal of Neuroscience Research 44 (4). 1996. 381-396.
Full Journal Title: Journal of Neuroscience Research
ISSN: 0360-4012
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 002 Ref. 021885

12/3/6 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13006475 BIOSIS Number: 99006475
Neonatal peptide exposure can prime T cells and, upon subsequent immunization, induce their immune deviation: Implications for antibody vs. T cell-mediated autoimmunity
Singh R R; Hahn B H; Sercarz E E
UCLA Dep. Med./Rheumatol., 32-47 Rehabilitation Cent., Box 951670, Los Angeles, CA 90095-1670, USA
Journal of Experimental Medicine 183 (4). 1996. 1613-1621.
Full Journal Title: Journal of Experimental Medicine
ISSN: 0022-1007
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 001 Ref. 006475

12/3/7 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

11807413 BIOSIS Number: 98407413
Prevention of Experimental Allergic Encephalomyelitis in Rats by

Targeting Autoantigen to B Cells: Evidence That the Protective Mechanism Depends on Changes in the Cytokine Response and Migratory Properties of the Autoantigen-specific T Cells
Saoudi A; Simmonds S; Huitinga I; Mason D
Med. Res. Council Cell. Immunol. Unit, Sir William Dunn Sch. Pathol., Univ. Oxford, Oxford OX1 3RE, UK
Journal of Experimental Medicine 182 (2). 1995. 335-344.
Full Journal Title: Journal of Experimental Medicine
ISSN: 0022-1007
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 006 Ref. 085005

12/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

11296596 BIOSIS Number: 97496596
Induction of interferon-gamma, interleukin-4, and transforming growth factor-beta in rats orally tolerized against experimental autoimmune myasthenia gravis
Wang Z-Y; Link H; Ljungdahl A; Hojeberg B; Link J; He B; Qiao J; Melms A; Olsson T
Dep. Biochem., CBS, Univ. Minnesota, 1479 Gortner Ave, St. Paul, MN 55108, USA
Cellular Immunology 157 (2). 1994. 353-368.
Full Journal Title: Cellular Immunology
ISSN: 0008-8749
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 010 Ref. 132335

12/3/9 (Item 9 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

11085011 BIOSIS Number: 97285011
Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM: Therapeutic intervention by immunostimulation?
Rabinovitch A
Room 430, Heritage Med. Res. Centre, Univ. Alberta, Edmonton, AB T6G 2S2, CAN
Diabetes 43 (5). 1994. 613-621.
Full Journal Title: Diabetes
ISSN: 0012-1797
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 001 Ref. 006656

12/3/10 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

10122951 EMBASE No: 96305115
IL-10 fails to abrogate experimental autoimmune encephalomyelitis
Cannella B.; Gao Y.L.; Brosnan C.; Raine C.S.
Dept. of Pathology (Neuropathology), Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461 USA

Journal of Neuroscience Research (USA) , 1996, 45/6 (735-746) CODEN: JNRED ISSN: 0360-4012
LANGUAGES: English SUMMARY LANGUAGES: English

12/3/11 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

10031902 EMBASE No: 96208172
Relationship between Th1/Th2 cytokine patterns and the arthritogenic response in collagen-induced arthritis
Mauri C.; Williams R.O.; Walmsley M.; Feldmann M.
Kennedy Institute of Rheumatology, 1 Lurgan Avenue, Hammersmith, London W6 8LW United Kingdom
European Journal of Immunology (Germany) , 1996, 26/7 (1511-1518) CODEN: EJIMA ISSN: 0014-2980
LANGUAGES: English SUMMARY LANGUAGES: English

12/3/12 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

9884696 EMBASE No: 96058832
TH1-TH2 cells in allergic responses: At the limits of a concept
Aebischer I.; Stadler B.M.
Inst. of Immunology and Allergology, University of Bern, Inselspital, CH-3010 Bern Switzerland
Advances in Immunology (USA) , 1996, 61 (341-403) CODEN: ADIMA ISSN: 0065-2776
LANGUAGES: English

12/3/13 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

9749569 EMBASE No: 95303400
Self-antigen-induced Th2 responses in experimental allergic encephalomyelitis (EAE)-resistant mice: Th2-mediated suppression of autoimmune disease
Cua D.J.; Hinton D.R.; Stohlman S.A.
MHC 142, USC School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033 USA
Journal of Immunology (USA) , 1995, 155/8 (4052-4059) CODEN: JOIMA ISSN: 0022-1767
LANGUAGES: English SUMMARY LANGUAGES: English

12/3/14 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

9586511 EMBASE No: 95150201
Tolerogenic forms of auto-antigens and cytokines in the induction of resistance to experimental allergic encephalomyelitis
Santambrogio L.; Crisi G.M.; Leu J.; Hochwald G.M.; Ryan T.; Thorbecke

G.J.
Department of Pathology, New York University Medical Center, 550 First Avenue, New York, NY 10016 USA
Journal of Neuroimmunology (Netherlands) , 1995, 58/2 (211-222) CODEN: JNRID ISSN: 0165-5728
LANGUAGES: English SUMMARY LANGUAGES: English

12/3/15 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

9579929 EMBASE No: 95144981
Etiology of idiopathic male infertility - New murine experimental autoimmune orchitis
Tokunaga Y.; Hiramine C.
Department of Urology, Kawasaki Medical School, Kurashiki Japan
Nishinihon Journal of Urology (Japan) , 1995, 57/4 (399-406) CODEN: NHJUA ISSN: 0029-0726
LANGUAGES: Japanese SUMMARY LANGUAGES: English

12/3/16 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

9198902 EMBASE No: 94131035
Oral tolerance: Immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens
Weiner H.L.; Friedman A.; Miller A.; Khoury S.J.; Al-Sabbagh A.; Santos L.; Sayegh M.; Nussenblatt R.B.; Trentham D.E.; Hafler D.A.
Center for Neurologic Diseases, Brigham and Women's Hospital, Beth Israel Hosp./Harvard Med. Sch., Boston, MA 02115 USA
ANNU. REV. IMMUNOL. (USA) , 1994, 12/- (809-837) CODEN: ARIMD ISSN: 0732-0582
LANGUAGES: English SUMMARY LANGUAGES: English

12/3/17 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus
(c)1997 Japan Science and Tech Corp(JST). All rts. reserv.

02651695 JICST ACCESSION NUMBER: 95A0444497 FILE SEGMENT: JICST-E
Recent Trends in the Treatment of Male Infertility. Etiology of Idiopathic Male Infertility-New Murine Experimental Autoimmune Orchitis.
TOKUNAGA YO (1); HIRAMINE CHIHARU (2)
(1) Kawasaki Med. Sch.; (2) Kagawa Med. Sch.
Nishinippon Hinyokika(Nishinihon Journal of Urology), 1995, VOL.57,NO.4, PAGE.399-406, FIG.5, TBL.3, REF.16
JOURNAL NUMBER: Z0253BAE ISSN NO: 0029-0726
UNIVERSAL DECIMAL CLASSIFICATION: 616.6-09
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication

12/3/18 (Item 1 from file: 144)

DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

12651402 PASCAL No.: 96-0345806
Immununization of non-obese diabetic (NOD) mice with glutamic acid decarboxylase-derived peptide 524-543 reduces cyclophosphamide-accelerated diabetes
SAI P; RIVEREAU A S; GRANIER C; HAERTLE T; MARTIGNAT L
Laboratory of Cellular and Molecular Immuno-endocrinology associated with INRA/ENVN, University School of Medicine, Nantes, France; CNRS UMR 9921, University of Montpellier, Montpellier, France; INRA La Geraudiere, Nantes, France
Journal: Clinical and experimental immunology, 1996, 105 (2) 330-337
Language: English

12/3/19 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal
(c) 1996 INIST/CNRS. All rts. reserv.

11899587 PASCAL No.: 95-0065930
Fonction des cellules T CD4 SUP + autoreactives dans deux modeles d'autoimmunite chez le rat
(Role of autoreactive CD4 SUP + T cells in two experimentally-induced immune disorders in the rat)
CASTEDO MariaDolores; PELLETIER Lucette, dir
Universite de Paris 07, Francee
Univ.: Universite de Paris 07. FRA Degree: Th. doct.
1993-11; 1993 206 p.
Language: French Summary Language: French; English

12/3/20 (Item 1 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01646642 SUPPLIER NUMBER: 18732757 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The hsp60 peptide p277 arrests the autoimmune diabetes induced by the toxin streptozotocin.
Elias, Dana; Cohen, Irun R.
Diabetes, v45, n9, p1168(5)
Sep, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3933 LINE COUNT: 00307

12/3/21 (Item 2 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01646639 SUPPLIER NUMBER: 18732754 (USE FORMAT 7 OR 9 FOR FULL TEXT)
T-cell responses to autoantigens in IDDM: the search for the Holy Grail.
Roep, Bart O.
Diabetes, v45, n9, p1147(10)
Sep, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional

WORD COUNT: 10850 LINE COUNT: 00890

12/3/22 (Item 3 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01634207 SUPPLIER NUMBER: 18589645 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Beta-cell destruction may be a late consequence of the autoimmune process
in nonobese diabetic mice.
Shimada, Akira; Charlton, Brett; Taylor-Edwards, Cariel; Fathman, C.
Garrison
Diabetes, v45, n8, p1063(5)
August, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3977 LINE COUNT: 00330

12/3/23 (Item 4 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01621873 SUPPLIER NUMBER: 18403837 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Genetic absence of gamma-interferon delays but does not prevent diabetes in
NOD mice.
Hultgren, Bruce; Huang, Xiaojian; Dybdal, Noel; Stewart, Timothy A.
Diabetes, v45, n6, p812(6)
June, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 5085 LINE COUNT: 00418

12/3/24 (Item 5 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01621864 SUPPLIER NUMBER: 18403827 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Cytokine gene expression in pancreatic islet-infiltrating leukocytes of BB
rats: expression of Th1 cytokines correlates with beta-cell destructive
insulitis and IDDM.(insulin-dependent diabetes mellitus)
Rabinovitch, Alex; Suarez-Pinzon, Wilma; El-Sheikh, Amr; Sorenson, Ole;
Power, Robert F.
Diabetes, v45, n6, p749(6)
June, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 3486 LINE COUNT: 00282

12/3/25 (Item 6 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01616174 SUPPLIER NUMBER: 18203039 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Facilitated DNA vaccine developed for herpes simplex virus.
DeNoon, Daniel J.

AIDS Weekly Plus, p4(3)
April 8, 1996
ISSN: 1069-1456 LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 491 LINE COUNT: 00046

12/3/26 (Item 7 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01608355 SUPPLIER NUMBER: 17838968 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Aberrant activation of CD8+ T-cell and CD8+ T-cell subsets in patients with newly diagnosed IDDM. (insulin-dependent diabetes mellitus)
Hehmke, Bernd; Michaelis, Dietrich; Gens, Elke; Laube, Frank; Kohnert, Klaus-Dieter
Diabetes, v44, n12, p1414(6)
Dec, 1995
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 5653 LINE COUNT: 00489

12/3/27 (Item 8 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01600693 SUPPLIER NUMBER: 17218599 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Comparative study of the protective effect afforded by intravenous administration of bovine or ovine insulin to young NOD mice.
Hutchings, Patricia R.; Cooke, Anne
Diabetes, v44, n8, p906(5)
August, 1995
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3401 LINE COUNT: 00286

12/3/28 (Item 9 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01599802 SUPPLIER NUMBER: 17314570 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The prevention of IDDM: injecting insulin into the cytokine network.(insulin dependent diabetes mellitus)(Letter to the Editor)
Gladstone, Paul; Nepon, Gerald T.
Diabetes, v44, n7, p859(4)
July, 1995
DOCUMENT TYPE: Letter to the Editor PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English RECORD TYPE: Fulltext
TARGET AUDIENCE: Professional
WORD COUNT: 3584 LINE COUNT: 00320

12/3/29 (Item 10 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01592689 SUPPLIER NUMBER: 16860566 (USE FORMAT 7 OR 9 FOR FULL TEXT)

Major role seen for IL-12 as vaccine adjuvant. (interleukin 12)
DeNoon, Daniel J.
AIDS Weekly, p6(2)
April 17, 1995
PUBLICATION FORMAT: Newsletter   ISSN: 1069-1456   LANGUAGE: English
RECORD TYPE: Fulltext   TARGET AUDIENCE: Professional
WORD COUNT: 483   LINE COUNT: 00045

12/3/30   (Item 11 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01497540   SUPPLIER NUMBER: 15981856   (USE FORMAT 7 OR 9 FOR FULL TEXT)
Immunization with the larger isoform of mouse glutamic acid decarboxylase (GAD67) prevents autoimmune diabetes in NOD mice. (non-obese diabetic mice)
Elliott, John F.; Qin, Hui-Yu; Bhatti, Sunita; Smith, Dean K.; Singh, Raj Kumari; Dillon, Tom; Lauzon, Jana; Singh, Bhagirath
Diabetes, v43, n12, p1494(6)
Dec, 1994
PUBLICATION FORMAT: Magazine/Journal   ISSN: 0012-1797   LANGUAGE: English
RECORD TYPE: Fulltext   TARGET AUDIENCE: Professional
WORD COUNT: 5036   LINE COUNT: 00414

12/3/31   (Item 12 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01496908   SUPPLIER NUMBER: 15949333   (USE FORMAT 7 OR 9 FOR FULL TEXT)
Cellular immune response to common mycobacterial antigens in subjects seropositive for Trypanosoma cruzi. (a protozoa that causes Chagas' disease)
Bottasso, O.A.; Ingledew, N.; Keni, M.; Morini, J.; Pividori, J.F.; Rook, G.A.W.; Stanford, J.L.
The Lancet, v344, n8936, p1540(2)
Dec 3, 1994
PUBLICATION FORMAT: Magazine/Journal   ISSN: 0099-5355   LANGUAGE: English
RECORD TYPE: Fulltext; Abstract   TARGET AUDIENCE: Professional
WORD COUNT: 1172   LINE COUNT: 00097

12/3/32   (Item 13 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01489224   SUPPLIER NUMBER: 15798980   (USE FORMAT 7 OR 9 FOR FULL TEXT)
Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis.
Chen, Youhai; Kuchroo, Vijay K.; Inobe, Jun-ichi; Hafler, David A.; Weiner, Howard L.
Science, v265, n5176, p1237(4)
August 26, 1994
PUBLICATION FORMAT: Magazine/Journal   ISSN: 0036-8075   LANGUAGE: English
RECORD TYPE: Fulltext; Abstract   TARGET AUDIENCE: Academic
WORD COUNT: 2989   LINE COUNT: 00238

12/3/33 (Item 14 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01424304 SUPPLIER NUMBER: 14105587 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The 12th International Immunology and Diabetes Workshop: Orlando, Florida.
Maclaren, Noel; Lafferty, Kevin
Diabetes, v42, n8, p1099(6)
August, 1993
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4432 LINE COUNT: 00440

12/3/34 (Item 15 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01310824 SUPPLIER NUMBER: 11562062 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The fail-safe paradigm of immunological self-tolerance.
Kroemer, Guido; Martinez-A, Carlos
The Lancet, v338, n8777, p1246(4)
Nov 16, 1991
PUBLICATION FORMAT: Magazine/Journal ISSN: 0099-5355 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 2211 LINE COUNT: 00250

12/3/35 (Item 16 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01240116 SUPPLIER NUMBER: 09184347 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Homology of cytokine synthesis inhibitory factor (IL-10) to the
Epstein-Barr virus gene BCRFI.
Moore, Kevin W.; Vieira, Paulo; Fiorentino, David F.; Trounstine, Mary L.;
Khan, Tariq A.; Mosmann, Timothy R.
Science, v248, n4960, p1230(5)
June 8, 1990
PUBLICATION FORMAT: Magazine/Journal ISSN: 0036-8075 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Academic
WORD COUNT: 3120 LINE COUNT: 00286

12/3/36 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

09882852 96404452
Interferon beta in multiple sclerosis.
Arnason BG
Pritzker School of Medicine and the Brain Research Institute, University
of Chicago, Illinois 60637, USA.
Clin Immunol Immunopathol (UNITED STATES) Oct 1996, 81 (1) p1-11,
ISSN 0090-1229 Journal Code: DEA
Contract/Grant No.: PO1 NS 24575, NS, NINDS
Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC

12/3/37 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

09833431 96355031
Recombinant IL-4 aggravates experimental autoimmune uveoretinitis in rats.
Ramanathan S; de Kozak Y; Saoudi A; Goureau O; Van der Meide PH; Druet P; Bellon B
INSERM Unit 430, Broussais Hospital, Paris, France.
J Immunol (UNITED STATES) Sep 1 1996, 157 (5) p2209-15, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/38 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

09833400 96355000
Short term treatment with soluble neuroantigen and anti-CD11a (LFA-1) protects rats against autoimmune encephalomyelitis: treatment abrogates autoimmune disease but not autoimmunity.
Willenborg DO; Staykova MA; Miyasaka M
Woden Valley Hospital, Canberra, Australia.
J Immunol (UNITED STATES) Sep 1 1996, 157 (5) p1973-80, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/39 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

09638118 96159718
Regulation of interleukin-4 activity by soluble interleukin-4 receptors.
Enssle K; Schulz G
Research Laboratories Behringwerke AG, Marburg, Germany.
J Clin Lab Anal (UNITED STATES) 1995, 9 (6) p450-5, ISSN 0887-8013 Journal Code: JLA
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

12/3/40 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

09546062 96067662
Suppression of murine experimental autoimmune thyroiditis by oral administration of porcine thyroglobulin.
Peterson KE; Braley-Mullen H
Department of Molecular Microbiology and Immunology, University of

Missouri, Columbia 65212, USA.
Cell Immunol (UNITED STATES) Nov 1995, 166 (1) p123-30, ISSN 0008-8749 Journal Code: CQ9
Contract/Grant No.: DK 35527, DK, NIDDK; T32 AI 27276, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/41 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

09447374 95377374
Presence of hsp65 in bacterial extracts (OM-89): a possible mediator of orally-induced tolerance?
Polla BS; Baladi S; Fuller K; Rook G
Allergy Unit, University Hospital, Geneva, Switzerland.
Experientia (SWITZERLAND) Aug 16 1995, 51 (8) p775-9, ISSN 0014-4754
Journal Code: EQZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/42 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

08907204 94222204
Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM. Therapeutic intervention by immunostimulation? [see comments]
Rabinovitch A
Department of Medicine, University of Alberta, Edmonton, Canada.
Diabetes (UNITED STATES) May 1994, 43 (5) p613-21, ISSN 0012-1797
Journal Code: E8X
Comment in Diabetes 1995 Jul;44(7):859-62
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC

12/3/43 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1996 Knight-Ridder Info. All rts. reserv.

07924815 92062815
Cyclosporine-induced autoimmunity and immune hyperreactivity.
Prud'homme GJ; Parfrey NA; Vanier LE
Department of Pathology, McGill University, Montreal, Quebec, Canada.
Autoimmunity (SWITZERLAND) 1991, 9 (4) p345-56, ISSN 0891-6934
Journal Code: A5H
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC

12/3/44 (Item 1 from file: 172)
DIALOG(R)File 172:EMBASE Alert
(c) 1996 Elservier Science B.V. All rts. reserv.

00215348 EMBASE No: 96305451

Both CD4sup + and CD8sup + T-cells in syngeneic islet grafts in NOD mice produce interferon-gamma during beta-cell destruction
Suarez-Pinzon W.; Rajotte R.V.; Mosmann T.R.; Rabinovitch A.
430 Heritage Medical Research Centre, University of Alberta, Edmonton, Alta. T6G 2S2 Canada
Diabetes (USA) , 1996
Vol/Iss/Pg: 45/10 (1350-1357) CODEN: DIAEA ISSN: 0012-1797
LANGUAGES: English SUMMARY LANGUAGES: English

12/3/45 (Item 1 from file: 211)
DIALOG(R)File 211:IAC NewSearch(TM)
(c) 1997 Info. Access Co. All rts. reserv.

06958053 Supplier Number: 18963516 (Use format 7 or 9 for FULL TEXT)
The pathogenesis of tuberculosis.
Rook, G.A.W.; Hernandez-Pando, Rogelio
Annual Review of Microbiology, v50, p259(26)
Annual, 1996
ISSN: 0066-4227 LANGUAGE: English RECORD TYPE: Fulltext; Abstract
WORD COUNT: 10337 LINE COUNT: 00850

12/3/46 (Item 1 from file: 377)
DIALOG(R)File 377:Derwent Drug File
(c) 1997 Derwent Info Ltd. All rts. reserv.

00715386 DERWENT ACCESSION NUMBER: 96-44012
Suppressive effects of a new anti-rheumatic drug T-614 on TH1 and TH2 T cell-mediated autoimmune animal models.
Aikawa Y; Tanuma N; Kojima T; Matsumoto Y; Makino S; Tanaka K
Toyama-Chem. (Toyama; Fuchu, Jap.)
Arthritis Rheum. 39, No. 9, Suppl., S126, 1996

12/3/47 (Item 2 from file: 377)
DIALOG(R)File 377:Derwent Drug File
(c) 1997 Derwent Info Ltd. All rts. reserv.

00677734 DERWENT ACCESSION NUMBER: 96-08603
Interleukin-12: An integral cytokine in the immune response.
Stern A S; Magram J; Presky D H
Roche (Nutley, N.J., USA)
Life Sci. 58, No. 8, 639-54, 1996

12/3/48 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15291134 Genuine Article#: VX173 No. References: 26
Title: ANTIIDIOTYPIC T-CELLS IN EARLY STAGES OF MYASTHENIA-GRAVIS - INCREASE IN THE NUMBER AND PREVALENCE CORRELATED TO CLINICAL IMPROVEMENT IN PATIENTS
Author(s): YI Q; PIRSKANEN R; LEFVERT AK
Corporate Source: KAROLINSKA HOSP,DEPT MED,IMMUNOL RES LAB/S-17176 STOCKHOLM//SWEDEN/; SODER SJUKHUSET,DEPT NEUROL/STOCKHOLM//SWEDEN/
Journal: SCANDINAVIAN JOURNAL OF IMMUNOLOGY, 1996, V44, N6 (DEC), P630-637

ISSN: 0300-9475
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/49 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15273298 Genuine Article#: VV440 No. References: 38
Title: ACTIVATION PATTERNS OF MURINE B-CELLS AFTER ORAL-ADMINISTRATION OF AN ENCAPSULATED SOLUBLE-ANTIGEN (VOL 14, PG 42, 1996)
Author(s): JAIN SL; BARONE KS; FLANAGAN MP; MICHAEL JG
Corporate Source: UNIV CINCINNATI,DEPT MOL GENET BIOCHEM & MICROBIOL/CINCINNATI//OH/45267; UNIV CINCINNATI,DEPT MOL GENET BIOCHEM & MICROBIOL/CINCINNATI//OH/45267
Journal: VACCINE, 1996, V14, N13 (SEP), P1291-1297
ISSN: 0264-410X
Language: ENGLISH Document Type: CORRECTION, ADDITION (Abstract Available)

12/3/50 (Item 3 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15205328 Genuine Article#: VQ338 No. References: 38
Title: ANTI-CD8 TREATMENT REDUCES THE SEVERITY OF INFLAMMATORY ARTHRITIS, BUT NOT VASCULITIS, IN MERCURIC CHLORIDE-INDUCED AUTOIMMUNITY
Author(s): KIELY PDW; OBRIEN D; OLIVEIRA DBG
Corporate Source: ST GEORGE HOSP,SCH MED,DIV RENAL MED,CRANMER TERRACE/LONDON SW17 0RE//ENGLAND/; ST GEORGE HOSP,SCH MED,DIV RENAL MED/LONDON SW17 0RE//ENGLAND/
Journal: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, 1996, V106, N2 (NOV), P 280-285
ISSN: 0009-9104
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/51 (Item 4 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15174475 Genuine Article#: VP226 No. References: 49
Title: SOLUBLE-PROTEIN BUT NOT PEPTIDE ADMINISTRATION DIVERTS THE IMMUNE-RESPONSE OF A CLONAL CD4+ T-CELL POPULATION TO THE T-HELPER-2 CELL PATHWAY
Author(s): DEGERMANN S; PRIA E; ADORINI L
Journal: JOURNAL OF IMMUNOLOGY, 1996, V157, N8 (OCT 15), P3260-3269
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/52 (Item 5 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15114554 Genuine Article#: VK244 No. References: 50
Title: CYTOKINES IN RELAPSING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS IN

DA RATS - PERSISTENT MESSENGER-RNA EXPRESSION OF PROINFLAMMATORY CYTOKINES AND ABSENT EXPRESSION OF INTERLEUKIN-10 AND TRANSFORMING GROWTH-FACTOR-BETA
Author(s): ISSAZADEH S; LORENTZEN JC; MUSTAFA MI; HOJEBERG B; MUSSENER A; OLSSON T
Corporate Source: KAROLINSKA INST,KAROLINSKA HOSP,DEPT MED,MOL MED UNIT/S-10401 STOCKHOLM//SWEDEN/; KAROLINSKA INST,KAROLINSKA HOSP,DEPT MED,MOL MED UNIT/S-10401 STOCKHOLM//SWEDEN/; KAROLINSKA INST,KAROLINSKA HOSP,DEPT RHEUMATOL/S-10401 STOCKHOLM//SWEDEN/
Journal: JOURNAL OF NEUROIMMUNOLOGY, 1996, V69, N1-2 (SEP), P103-115
ISSN: 0165-5728
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/53   (Item 6 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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15033202   Genuine Article#: VE109   No. References: 28
Title: IL-12 PROMOTES CELLULAR BUT NOT HUMORAL TYPE-II COLLAGEN-SPECIFIC T(H)1-TYPE RESPONSES IN C57BL/6 AND B10.Q MICE AND FAILS TO INDUCE ARTHRITIS
Author(s): SZELIGA J; HESS H; RUDE E; SCHMITT E; GERMANN T
Corporate Source: INST IMMUNOL,OBERE ZAHLBACHER STR 67/D-55101 MAINZ//GERMANY/; INST IMMUNOL/D-55101 MAINZ//GERMANY/
Journal: INTERNATIONAL IMMUNOLOGY, 1996, V8, N8 (AUG), P1221-1227
ISSN: 0953-8178
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/54   (Item 7 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15001317   Genuine Article#: VC337   No. References: 45
Title: BOTH CD4(+) AND CD8(+) T-CELLS ARE ESSENTIAL TO INDUCE EXPERIMENTAL AUTOIMMUNE MYASTHENIA-GRAVIS
Author(s): ZHANG GX; XIAO BG; BAKHIET M; VANDERMEIDE P; WIGZELL H; LINK H; OLSSON T
Corporate Source: HUDDINGE HOSP,DIV NEUROL/S-14186 HUDDINGE//SWEDEN/; BIOMED PRIMATE RES CTR/RIJSWIJK//NETHERLANDS/; KAROLINSKA INST,DIV IMMUNOL/STOCKHOLM//SWEDEN/; KAROLINSKA HOSP,MOL MED UNIT/STOCKHOLM//SWEDEN/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1996, V184, N2 (AUG 1), P349-356
ISSN: 0022-1007
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/55   (Item 8 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14991348   Genuine Article#: VB309   No. References: 43
Title: INDUCTION OF CLASS-II MAJOR HISTOCOMPATIBILITY COMPLEX BLOCKADE AS WELL AS T-CELL TOLERANCE BY PEPTIDES ADMINISTERED IN SOLUBLE FORM
Author(s): NIHIRA SI; FALCIONI F; JURETIC A; BOLIN D; NAGY ZA
Corporate Source: HOFFMANN LA ROCHE INC,DEPT INFLAMMAT AUTOIMMUNEDIS,BLDG 86 RM 602D,340 KINGSLAND ST/NUTLEY//NJ/07110; HOFFMANN LA ROCHE

INC,DEPT INFLAMMAT AUTOIMMUNEDIS/NUTLEY//NJ/07110
Journal: EUROPEAN JOURNAL OF IMMUNOLOGY, 1996, V26, N8 (AUG), P1736-1742
ISSN: 0014-2980
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/56   (Item 9 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14952832   Genuine Article#: UY893   No. References: 64
Title: IMMUNITY AGAINST YERSINIA-ENTEROCOLITICA BY VACCINATION WITH YERSINIA HSP60 IMMUNOSTIMULATING COMPLEXES OR YERSINIA HSP60 PLUS INTERLEUKIN-12
Author(s): NOLL A; AUTENRIETH IB
Corporate Source: UNIV WURZBURG,INST HYG & MIKROBIOL,JOSEF SCHNEIDER STR 2,BAU 17/D-97080 WURZBURG//GERMANY/; UNIV WURZBURG,INST HYG & MIKROBIOL/D-97080 WURZBURG//GERMANY/
Journal: INFECTION AND IMMUNITY, 1996, V64, N8 (AUG), P2955-2961
ISSN: 0019-9567
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/57   (Item 10 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14943866   Genuine Article#: UY134   No. References: 36
Title: ANTIGEN-DRIVEN PERIPHERAL IMMUNE TOLERANCE - SUPPRESSION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS AND COLLAGEN-INDUCED ARTHRITIS BY AEROSOL ADMINISTRATION OF MYELIN BASIC-PROTEIN OR TYPE-II COLLAGEN
Author(s): ALSABBAGH A; NELSON PA; AKSELBAND Y; SOBEL RA; WEINER HL
Corporate Source: BRIGHAM & WOMENS HOSP,CTR NEUROL DIS,DEPT NEUROL,221 LONGWOOD AVE/BOSTON//MA/02115; BRIGHAM & WOMENS HOSP,CTR NEUROL DIS,DEPT NEUROL/BOSTON//MA/02115; HARVARD UNIV,SCH MED/BOSTON//MA/02115 ; STANFORD UNIV,SCH MED,DEPT PATHOL/STANFORD//CA/94305; VET ADM MED CTR,LAB SERV/PALO ALTO//CA/94304; AUTOIMMUNE INC/LEXINGTON//MA/02173
Journal: CELLULAR IMMUNOLOGY, 1996, V171, N1 (JUL 10), P111-119
ISSN: 0008-8749
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/58   (Item 11 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14867115   Genuine Article#: UR954   No. References: 40
Title: DYNAMICS OF MESSENGER-RNA EXPRESSION OF INTERFERON-GAMMA, INTERLEUKIN-4 AND TRANSFORMING GROWTH-FACTOR-BETA-1 IN SCIATIC-NERVES AND LYMPHOID ORGANS IN EXPERIMENTAL ALLERGIC NEURITIS
Author(s): ZHU J; MIX E; ISSAZADEH S; LINK H
Corporate Source: KAROLINSKA INST,HUDDINGE HOSP,DIV NEUROL/S-14186 HUDDINGE//SWEDEN/; KAROLINSKA HOSP,DEPT MED,MOLEC MED UNIT/S-10401STOCKHOLM//SWEDEN/
Journal: EUROPEAN JOURNAL OF NEUROLOGY, 1996, V3, N3 (MAY), P232-240
ISSN: 1351-5101
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/59 (Item 12 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14778111 Genuine Article#: UK974 No. References: 52
Title: INDUCTION OF PNEUMOCOCCAL POLYSACCHARIDE-SPECIFIC MUCOSAL IMMUNE-RESPONSES BY ORAL IMMUNIZATION
Author(s): VANCOTT JL; KOBAYASHI T; YAMAMOTO M; PILLAI S; MCGHEE JR; KIYONO H
Corporate Source: UNIV ALABAMA,DEPT MICROBIOL & ORAL BIOL,IMMUNOBIOL VACCINE CTR/BIRMINGHAM//AL/35294; UNIV ALABAMA,DEPT MICROBIOL & ORAL BIOL,IMMUNOBIOL VACCINE CTR/BIRMINGHAM//AL/35294; LEDERLE PRAXIS BIOL/W HENRIETTA//NY/14586; OSAKA UNIV,MICROBIAL DIS RES INST,DEPT MUCOSAL IMMUNOL/OSAKA//JAPAN/
Journal: VACCINE, 1996, V14, N5 (APR), P392-398
ISSN: 0264-410X
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/60 (Item 13 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14753751 Genuine Article#: UJ246 No. References: 77
Title: POTENTIAL FOR DIRECTING APPROPRIATE RESPONSES TO VACCINES BY CYTOKINE MANIPULATION
Author(s): TANG YW; GRAHAM BS
Corporate Source: VANDERBILT UNIV,SCH MED,DEPT MED,DIV INFECT DIS,A-3310 MCN/NASHVILLE//TN/37232; VANDERBILT UNIV,SCH MED,DEPT MICROBIOL & IMMUNOL/NASHVILLE//TN/37232
Journal: CLINICAL IMMUNOTHERAPEUTICS, 1996, V5, N5 (MAY), P327-333
ISSN: 1172-7039
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/61 (Item 14 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14719353 Genuine Article#: UG365 No. References: 38
Title: ORAL IMMUNIZATION OF INTERLEUKIN-4 (IL-4) KNOCKOUT MICE WITH A RECOMBINANT SALMONELLA STRAIN OR CHOLERA-TOXIN REVEALS THAT CD4(+) TH2 CELLS PRODUCING IL-6 AND IL-10 ARE ASSOCIATED WITH MUCOSAL IMMUNOGLOBULIN-A RESPONSES
Author(s): OKAHASHI N; YAMAMOTO M; VANCOTT JL; CHATFIELD SN; ROBERTS M; BLUETHMANN H; HIROI T; KIYONO H; MCGHEE JR
Corporate Source: UNIV ALABAMA,IMMUNOBIOL VACCINE CTR,DEPT MICROBIOL,BBRB 761/BIRMINGHAM//AL/35294; UNIV ALABAMA,IMMUNOBIOL VACCINE CTR,DEPT MICROBIOL/BIRMINGHAM//AL/35294; UNIV ALABAMA,MED CTR,DEPT ORAL BIOL/BIRMINGHAM//AL/35294; UNIV ALABAMA,MED CTR,MUCOSAL IMMUNIZAT RES GRP/BIRMINGHAM//AL/35294; UNIV LONDON IMPERIAL COLL SCI TECHNOL & MED,DEPT BIOCHEM,MEDEVA,VACCINE RES UNIT/LONDON SW7 2AY//ENGLAND/; UNIV GLASGOW,DEPT VET PATHOL/GLASGOW G61 1QH/LANARK/SCOTLAND/; HOFFMANN LA ROCHE AG/CH-4002 BASEL//SWITZERLAND/; OSAKA UNIV,MICROBIAL DIS RES INST,DEPT MUCOSAL IMMUNOL/SUITA/OSAKA 565/JAPAN/
Journal: INFECTION AND IMMUNITY, 1996, V64, N5 (MAY), P1516-1525

ISSN: 0019-9567
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/62   (Item 15 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14681479   Genuine Article#: UD973   No. References: 52
Title: ALPHA/BETA-T CELL RECEPTOR-DIRECTED THERAPY IN RAT ALLOGRAFT RECIPIENTS - LONG-TERM SURVIVAL OF CARDIAC ALLOGRAFTS AFTER PRETREATMENT WITH R73 MAB IS ASSOCIATED WITH UP-REGULATION OF TH2-TYPE CYTOKINES
Author(s): HEIDECKE CD; HANCOCK WW; WESTERHOLT S; SEWCZIK T; JAKOBS F; ZANTL N; VARZARU A; SIEGLING A; KURRLE R; DEUSCH K; VOLK HD; KUPIECWEGLINSKI JW
Corporate Source: KLINIKUM RECHTS DER ISAR,DEPT SURG,ISMANINGER STR 22/D-81675 MUNICH//GERMANY/; TECH UNIV MUNICH,KLINIKUM RECHTS ISAR,DEPT SURG/D-82675 MUNICH//GERMANY/; MONASH UNIV SCH MED,DEPT PATHOL & IMMUNOL/PRAHRAN/VIC/AUSTRALIA/; HUMBOLDT UNIV BERLIN,INST MED IMMUNOL CHARITE/D-10098 BERLIN//GERMANY/; BEHRING WERKE/D-35041 MARBURG//GERMANY/; TECH UNIV MUNICH,KLINIKUM RECHTS ISAR,DEPT MED/D-81675 MUNICH//GERMANY/; HARVARD UNIV,SCH MED,SURG RES LAB/BOSTON//MA/02115; TECH UNIV MUNICH,DEPT SURG/D-81675 MUNICH//GERMANY/
Journal: TRANSPLANTATION, 1996, V61, N6 (MAR 27), P948-956
ISSN: 0041-1337
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/63   (Item 16 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14671744   Genuine Article#: UD138   No. References: 35
Title: HIGH-DOSES OF INTERLEUKIN-12 INHIBIT THE DEVELOPMENT OF JOINT DISEASE IN DBA/1 MICE IMMUNIZED WITH TYPE-II COLLAGEN IN COMPLETE FREUNDS-ADJUVANT
Author(s): HESS H; GATELY MK; RUDE E; SCHMITT E; SZELIGA J; GERMANN T
Corporate Source: INST IMMUNOL,OBERE ZAHLBACHER STR 67/D-55101 MAINZ//GERMANY/; INST IMMUNOL/D-55101 MAINZ//GERMANY/; HOFFMANN LA ROCHE INC,DEPT INFLAMMAT AUTOIMMUNEDIS/NUTLEY//NJ/07110
Journal: EUROPEAN JOURNAL OF IMMUNOLOGY, 1996, V26, N1 (JAN), P187-191
ISSN: 0014-2980
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/64   (Item 17 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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14551908   Genuine Article#: TW130   No. References: 43
Title: CD8-DEFICIENT MICE EXHIBIT AUGMENTED MUCOSAL IMMUNE-RESPONSES AND INTACT ADJUVANT EFFECTS TO CHOLERA-TOXIN
Author(s): HORNQUIST E; GRDIC D; MAK T; LYCKE N
Corporate Source: GOTHENBURG UNIV,DEPT MED MICROBIOL & IMMUNOL/S-41346 GOTHENBURG//SWEDEN/; GOTHENBURG UNIV,DEPT MED MICROBIOL & IMMUNOL/S-41346 GOTHENBURG//SWEDEN/; UNIV TORONTO,ONTARIO CANC

INST/TORONTO/ON M5S 1A1/CANADA/; UNIV TORONTO,DEPT MED BIOPHYS/TORONTO/ON M5S 1A1/CANADA/; UNIV TORONTO,DEPT IMMUNOL/TORONTO/ON M5S 1A1/CANADA/
Journal: IMMUNOLOGY, 1996, V87, N2 (FEB), P220-229
ISSN: 0019-2805
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/65   (Item 18 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14534503   Genuine Article#: TW109   No. References: 51
Title: SELECTIVE DEVELOPMENT OF T-HELPER (TH)2 CELLS INDUCED BY CONTINUOUS ADMINISTRATION OF LOW-DOSE SOLUBLE-PROTEINS TO NORMAL AND BETA-2-MICROGLOBULIN-DEFICIENT BALB/C MICE
Author(s): GUERY JC; GALBIATI F; SMIROLDO S; ADORINI L
Corporate Source: ROCHE MILANO RIC,VIA OLGETTINA 58/I-20132 MILAN//ITALY/; ROCHE MILANO RIC/I-20132 MILAN//ITALY/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1996, V183, N2 (FEB 1), P485-497
ISSN: 0022-1007
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/66   (Item 19 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14500035   Genuine Article#: TR930   No. References: 179
Title: IMMUNOPATHOGENESIS OF JUVENILE RHEUMATOID-ARTHRITIS - ROLE OF T-CELLS AND MHC
Author(s): SAKKAS LI; PLATSOUCAS CD
Corporate Source: TEMPLE UNIV,SCH MED,DEPT MICROBIOL & IMMUNOL,3400 N BROAD ST/PHILADELPHIA//PA/19140; TEMPLE UNIV,SCH MED,DEPT MICROBIOL & IMMUNOL/PHILADELPHIA//PA/19140
Journal: IMMUNOLOGIC RESEARCH, 1995, V14, N3, P218-236
ISSN: 0257-277X
Language: ENGLISH   Document Type: REVIEW   (Abstract Available)

12/3/67   (Item 20 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14480439   Genuine Article#: TR327   No. References: 37
Title: ORAL ANTIGEN INHIBITS PRIMING OF CD8(+) CTL, CD4(+) T-CELLS, AND ANTIBODY-RESPONSES WHILE ACTIVATING CD8(+) SUPPRESSOR T-CELLS
Author(s): KE Y; KAPP JA
Corporate Source: EMORY UNIV,SCH MED,DEPT PATHOL,S CLIN BLDG,ROOM4215,1327 CLIFTON RD NE/ATLANTA//GA/30322; EMORY UNIV,SCH MED,DEPT PATHOL/ATLANTA//GA/30322; EMORY UNIV,SCH MED,WINSHIP CANC CTR/ATLANTA//GA/30322
Journal: JOURNAL OF IMMUNOLOGY, 1996, V156, N3 (FEB 1), P916-921
ISSN: 0022-1767
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/68   (Item 21 from file: 434)

DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14312675 Genuine Article#: TD021 No. References: 71
Title: CYTOKINE-MEDIATED EFFECTS IN MUCOSAL IMMUNITY
Author(s): KRAMER DR; SUTHERLAND RM; BAO S; HUSBAND AJ
Corporate Source: UNIV SYDNEY,DEPT VET PATHOL/SYDNEY/NSW 2006/AUSTRALIA/; UNIV SYDNEY,DEPT VET PATHOL/SYDNEY/NSW 2006/AUSTRALIA/
Journal: IMMUNOLOGY AND CELL BIOLOGY, 1995, V73, N5 (OCT), P389-396
ISSN: 0818-9641
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/69 (Item 22 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14226821 Genuine Article#: RX275 No. References: 121
Title: INTERLEUKIN-12
Author(s): GERMANN T; RUDE E
Corporate Source: INST IMMUNOL,OBERE ZAHLBACHER STR 67/D-55131 MAINZ//GERMANY/
Journal: INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY, 1995, V108, N2 (OCT), P103-112
ISSN: 1018-2438
Language: ENGLISH Document Type: REVIEW (Abstract Available)

12/3/70 (Item 23 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14033452 Genuine Article#: RL098 No. References: 41
Title: PREVENTION OF EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN RATS BY TARGETING AUTOANTIGEN TO CELLS - EVIDENCE THAT THE PROTECTIVE MECHANISM DEPENDS ON CHANGES IN THE CYTOKINE RESPONSE AND MIGRATORY PROPERTIES OF THE AUTOANTIGEN-SPECIFIC T-CELLS
Author(s): SAOUDI A; SIMMONDS S; HUITINGA I; MASON D
Corporate Source: UNIV OXFORD,SIR WILLIAM DUNN SCH PATHOL,MRC,CELLULAR IMMUNOL UNIT/OXFORD OX1 3RE//ENGLAND/; VRIJE UNIV AMSTERDAM,FAC MED,DEPT CELL BIOL & IMMUNOL/1081 BT AMSTERDAM//NETHERLANDS/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1995, V182, N2 (AUG 1), P335-344
ISSN: 0022-1007
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

12/3/71 (Item 24 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

13506490 Genuine Article#: PT680 No. References: 102
Title: IMMUNOTOXICITY OF SILICONE - IMPLICATIONS OF OXIDANT BALANCE TOWARDS ADJUVANT ACTIVITY
Author(s): YOSHIDA SH; TEUBER SS; GERMAN JB; GERSHWIN ME
Corporate Source: UNIV CALIF DAVIS,SCH MED,DIV RHEUMATOL ALLERGY & CLIN IMMUNOL/DAVIS//CA/95616; UNIV CALIF DAVIS,SCH MED,DIV RHEUMATOL ALLERGY & CLIN IMMUNOL/DAVIS//CA/95616; UNIV CALIF DAVIS,DEPT FOOD SCI & TECHNOL/DAVIS//CA/95616; NO CALIF SYST CLIN,VET ADM/PLEASANT

HILL//CA/94523
Journal: FOOD AND CHEMICAL TOXICOLOGY, 1994, V32, N11 (NOV), P1089-1100
ISSN: 0278-6915
Language: ENGLISH   Document Type: REVIEW   (Abstract Available)

12/3/72   (Item 25 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

13122146   Genuine Article#: NQ324   No. References: 31
Title: DIFFERENTIAL-EFFECTS OF OVAL VERSUS INTRATHYMIC ADMINISTRATION OF POLYMORPHIC MAJOR HISTOCOMPATIBILITY COMPLEX CLASS-II PEPTIDES ON MONONUCLEAR AND ENDOTHELIAL-CELL ACTIVATION AND CYTOKINE EXPRESSION DURING A DELAYED-TYPE HYPERSENSITIVITY RESPONSE
Author(s): HANCOCK WW; KHOURY SJ; CARPENTER CB; SAYEGH MH
Corporate Source: ALFRED HOSP,MONASH MED SCH,DEPT PATHOL & IMMUNOL,COMMERCIAL RD/PRAHRAN/VIC 3181/AUSTRALIA/; HARVARD UNIV,BRIGHAM & WOMENS HOSP,SCH MED,CTR NEUROL DIS/BOSTON//MA/00000; HARVARD UNIV,BRIGHAM & WOMENS HOSP,SCH MED,DEPTMED,DIV RENAL,IMMUNOGENET & TRANSPLANTAT LAB/BOSTON//MA/00000
Journal: AMERICAN JOURNAL OF PATHOLOGY, 1994, V144, N6 (JUN), P1149-1158
ISSN: 0002-9440
Language: ENGLISH   Document Type: NOTE   (Abstract Available)

12/3/73   (Item 26 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

12830617   Genuine Article#: MR810   No. References: 165
Title: ULTRASTRUCTURAL PATHOLOGY OF EXPERIMENTAL AUTOIMMUNE UVEITIS - A REVIEW
Author(s): MCMENAMIN PG; BROEKHUYSE RM; FORRESTER JV
Corporate Source: UNIV WESTERN AUSTRALIA,DEPT ANAT & HUMAN BIOL/PERTH/WA 6009/AUSTRALIA/; UNIV NIJMEGEN,INST OPHTHALMOL/6500 HB NIJMEGEN//NETHERLANDS/; UNIV ABERDEEN,SCH MED,DEPT OPHTHALMOL/FORESTERHILL AV9 2ZD//SCOTLAND/
Journal: MICRON, 1993, V24, N5, P521-546
ISSN: 0968-4328
Language: ENGLISH   Document Type: REVIEW   (Abstract Available)

12/3/74   (Item 27 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

12662351   Genuine Article#: MD953   No. References: 42
Title: IN-VIVO INDUCTION OF TOLERANCE IN MURINE CD4+ CELL SUBSETS
Author(s): ROMBALL CG; WEIGLE WO
Corporate Source: SCRIPPS CLIN & RES FDN,RES INST,DEPT IMMUNOL,IMM9,10666 N TORREY PINES RD/LA JOLLA//CA/92037; SCRIPPS CLIN & RES FDN,RES INST,DEPT IMMUNOL,IMM9,10666 N TORREY PINES RD/LA JOLLA//CA/92037
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1993, V178, N5 (NOV 1), P 1637-1644
ISSN: 0022-1007
Language: ENGLISH   Document Type: ARTICLE   (Abstract Available)

12/3/75 (Item 28 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

10934707 Genuine Article#: FU006 No. References: 152
Title: IFN-GAMMA, A LYMPHOKINE THAT MODULATES IMMUNOLOGICAL AND INFLAMMATORY RESPONSES
Author(s): LANDOLFO S; GAROTTA G
Corporate Source: UNIV TURIN,IST MICROBIOL,VIA SANTENA 9/I-10126 TURIN//ITALY/; F HOFFMANN LA ROCHE & CO LTD,CENT RES UNIT/CH-4002 BASEL//SWITZERLAND/
Journal: JOURNAL OF IMMUNOLOGICAL RESEARCH, 1991, V3, N2, P81-94
Language: ENGLISH Document Type: REVIEW (Abstract Available)

12/3/76 (Item 1 from file: 452)
DIALOG(R)File 452:Drug Data Report
(c) 1996 J.R. Prous S.A. All rts. reserv.

00164387

ENTRY NUMBER:	164387 (Actively Investigated)
COMPOUND TYPE:	Preferred
DRUG NAME:	CLMF
	IL-12
	NKSF
	rhIL-12
	Ro-24-7472
GENERIC NAME	Cytotoxic lymphocyte maturation factor
	Interleukin-12
	Natural killer stimulatory factor
DEVEL. PHASE:	Phase II
ORIGINATOR:	Genetics Inst.
	Roche
	Wistar Inst. Anatomy Biology
LICENSEE:	Wyeth-Ayerst
	Yamanouchi
CLASS:	62100 (Immunostimulant)
	71530 (Immunomodulator (AIDS))
	75000 (Antineoplastic)
	99000 (Biotechnology)

12/3/77 (Item 1 from file: 636)
DIALOG(R)File 636:IAC Newsletter DB(TM)
(c) 1997 Information Access Co. All rts. reserv.

03259419
Autoimmune Encephalomyelitis: Birnbaum, G.; Kotilinek, L.; Schlievert, P.; Clark, H.B.; Trotter, J.; Horvath, E.; Gao, E.; Cox, M.; Braun, P.E. "Heat Shock Proteins and Experimental Autoimmune Encephalomyelitis (EAE) .1. Immunization with a Peptide of the Myelin Protein 2',3' Cyclic Nucleotide 3' Phosphodiesterase That Is Cross-Reactive with a Heat Shock Protein Alters the Course of EAE."
Vaccine Weekly July 8, 1996
ISSN: 1074-2921 WORD COUNT: 327
PUBLISHER: Charles W Henderson

12/3/78 (Item 2 from file: 636)
DIALOG(R)File 636:IAC Newsletter DB(TM)
(c) 1997 Information Access Co. All rts. reserv.

02743265
Conference Coverage Major Role Seen for IL-12 as Vaccine Adjuvant
AIDS Weekly April 17, 1995
ISSN: 1069-1456 WORD COUNT: 499
PUBLISHER: CW Henderson, Publisher
?ds

Set	Items	Description
S1	0	TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
S2	1174	E1-E31
S3	129	E1-E14
S4	1303	S2 OR S3
S5	15	S4 AND TH2
S6	8	RD (unique items)
S7	23	TH2 AND AUTOIMMUN
S8	1403	TH2 AND AUTOIMMUN?
S9	120	S8 AND ADJUVANT?
S10	120	S9
S11	78	RD (unique items)
S12	78	S11 NOT S6

?t s12/9/70,30,16,14,13,9,8,7

12/9/70 (Item 23 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

14033452 Genuine Article#: RL098 Number of References: 41
Title: PREVENTION OF EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN RATS BY TARGETING AUTOANTIGEN TO CELLS - EVIDENCE THAT THE PROTECTIVE MECHANISM DEPENDS ON CHANGES IN THE CYTOKINE RESPONSE AND MIGRATORY PROPERTIES OF THE AUTOANTIGEN-SPECIFIC T-CELLS
Author(s): SAOUDI A; SIMMONDS S; HUITINGA I; MASON D
Corporate Source: UNIV OXFORD,SIR WILLIAM DUNN SCH PATHOL,MRC,CELLULAR IMMUNOL UNIT/OXFORD OX1 3RE//ENGLAND/; VRIJE UNIV AMSTERDAM,FAC MED,DEPT CELL BIOL & IMMUNOL/1081 BT AMSTERDAM//NETHERLANDS/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1995, V182, N2 (AUG 1), P335-344
ISSN: 0022-1007
Language: ENGLISH Document Type: ARTICLE
Geographic Location: ENGLAND; NETHERLANDS
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: IMMUNOLOGY; MEDICINE, RESEARCH & EXPERIMENTAL
Abstract: Previous experiments from this laboratory have shown that Lewis rats were protected from experimental allergic encephalomyelitis (EAE) induced by the injection of myelin basic protein (MBP) in Freund's complete adjuvant if they were treated with the encephalitogenic peptide of MBP covalently linked to mouse anti-rat immunoglobulin (Ig) D. It was suggested that this protection developed because the antibody-peptide conjugate targeted the peptide to B cells and that this mode of presentation induced a Th2-like T cell response that controlled the concomitant encephalitogenic Th1 reaction to the autoantigen. The current experiments were carried out to test this

hypothesis and to examine the alternative explanation for the protective effect of the conjugate pretreatment, namely that it induced a state of nonresponsiveness in the autoantigenspecific T cells. It was shown that EAE induction was suppressed in Lewis rats when the antibody-peptide conjugate was injected intravenously 14 and 7 d before immunization with MBP in adjuvant, but that anti-MBP antibody titers were at least as high in these animals as in controls that were not pretreated with the conjugate before immunization. Lymph node cells from these pretreated animals, while proliferating in vitro to MBP as vigorously as those from controls, produced less interferon gamma and were very inferior in their ability to transfer disease after this in vitro activation. In contrast, these same lymph node cells from protected rats generated markedly increased levels of messenger RNA for interleukin (IL)-4 and IL-13. When these in vitro experiments were repeated using the encephalitogenic peptide rather than MBP as the stimulus, the proliferative response of lymph node cells from pretreated donors was less than that from controls but was still readily detectable in the majority of experiments. Furthermore, the cytokine expression induced by the peptide was similar to that elicited by whole MBP. While these results support the original hypothesis that the anti-IgD-peptide conjugate pretreatment protected rats from EAE by inducing a Th2-type cytokine response, a totally unexpected finding was that this pretreatment greatly reduced the level of leukocyte infiltration into the central nervous system. This result provides a direct explanation for the protective effect of the pretreatment, but it raises questions regarding migratory and homing patterns of leukocytes activated by different immunological stimuli.
Identifiers--KeyWords Plus: DELAYED-TYPE HYPERSENSITIVITY; TH2 CLONES; MONOCLONAL-ANTIBODIES; IMMUNE-SYSTEM; MURINE TH1; B-CELLS; DISEASE; SUBSETS; LYMPHOCYTES; INDUCTION
Research Fronts: 93-2411 004 (RAT MICROGLIAL CELLS; CYTOKINE EXPRESSION OF MACROPHAGES; CULTURED ASTROCYTES; AUTOIMMUNE POTENTIAL; NEUROLOGICAL DISEASE; DIFFERENTIAL INDUCTION)
93-1130 002 (BCL-2 PROTOONCOGENE EXPRESSION; PROGRAMMED CELL-DEATH; AUTOANTIGEN INHIBITS APOPTOSIS)
93-3982 002 (BALB/C MICE; MURINE CUTANEOUS LEISHMANIASIS; TH1 CD4+ T-CELLS; CYTOKINE PATTERNS; GAMMA-INTERFERON RESPONSE; PREFERENTIAL INDUCTION)
93-3975 001 (TH2 CELLS; ANTICRYPTOCOCCAL DELAYED-TYPE HYPERSENSITIVITY RESPONSE; ALLERGIC DISEASES)
93-5718 001 (CD4+ T-CELLS; INTERLEUKIN-4 TRANSGENIC MICE; CYTOKINE PRODUCTION PROFILE)
93-7329 001 (MYELIN OLIGODENDROCYTE GLYCOPROTEIN; EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS; MACROPHAGES MICROGLIA; RAT MODEL; MAJOR HISTOCOMPATIBILITY COMPLEX)
Cited References:
ANDO DG, 1989, V124, P132, CELL IMMUNOL
BARCLAY AN, 1981, V42, P593, IMMUNOLOGY
BRIDEAU RJ, 1980, V10, P609, EUR J IMMUNOL
CHATELAIN R, 1992, V148, P1182, J IMMUNOL
CHER DJ, 1987, V138, P3688, J IMMUNOL
DAY MJ, 1992, V175, P655, J EXP MED
DIJKSTRA CD, 1985, V54, P589, IMMUNOLOGY
EYNON EE, 1992, V175, P131, J EXP MED
EYNON EE, 1993, V151, P2958, J IMMUNOL
FINKELMAN FD, 1986, V137, P2878, J IMMUNOL
FINKELMAN FD, 1987, V138, P2826, J IMMUNOL
FIORENTINO DF, 1989, V170, P2081, J EXP MED

GAJEWSKI TF, 1989, V111, P79, IMMUNOL REV
GAJEWSKI TF, 1991, V146, P1750, J IMMUNOL
GAJEWSKI TF, 1991, V142, P19, RES IMMUNOL
GILLIS S, 1978, V120, P2027, J IMMUNOL
GONATAS NK, 1986, V7, P121, IMMUNOL TODAY
HASHIM GA, 1978, V39, P60, IMMUNOL REV
HINRICHS DJ, 1981, V126, P1857, J IMMUNOL
HSIUNG LM, 1982, V203, P293, BIOCHEM J
ISSEKUTZ TB, 1988, V140, P2989, J IMMUNOL
LAKKIS FG, 1993, V197, P612, BIOCHEM BIOPH RES CO
MACPHEE IAM, 1989, V169, P431, J EXP MED
MASON D, 1991, V12, P57, IMMUNOL TODAY
MCKNIGHT AJ, 1991, V21, P1187, EUR J IMMUNOL
MCMASTER WR, 1979, V9, P426, EUR J IMMUNOL
MORRIS SC, 1994, V152, P3777, J IMMUNOL
MOSMANN TR, 1989, V7, P145, ANNU REV IMMUNOL
PEZZELLA F, 1990, V137, P225, AM J PATHOL
POWRIE F, 1993, V23, P3043, EUR J IMMUNOL
RACKE MK, 1994, V180, P1961, J EXP MED
RAINE CS, 1984, V50, P608, LAB INVEST
SADICK MD, 1990, V171, P115, J EXP MED
SCOTT P, 1989, V112, P161, IMMUNOL REV
SEDGWICK J, 1987, V165, P1058, J EXP MED
SEDGWICK JD, 1986, V13, P217, J NEUROIMMUNOL
SWAIN SL, 1991, V123, P115, IMMUNOL REV
VANDERVEEN RC, 1993, V48, P221, J NEUROIMMUNOL
WEKERLE H, 1986, V9, P271, TRENDS NEUROSCI
WILLIAMS AF, 1977, V12, P663, CELL
ZURAWSKI G, 1994, V15, P19, IMMUNOL TODAY

12/9/30 (Item 11 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01497540 SUPPLIER NUMBER: 15981856 (THIS IS THE FULL TEXT)
Immunization with the larger isoform of mouse glutamic acid decarboxylase (GAD67) prevents autoimmune diabetes in NOD mice. (non-obese diabetic mice)
Elliott, John F.; Qin, Hui-Yu; Bhatti, Sunita; Smith, Dean K.; Singh, Raj Kumari; Dillon, Tom; Lauzon, Jana; Singh, Bhagirath
Diabetes, v43, n12, p1494(6)
Dec, 1994
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 5036 LINE COUNT: 00414

TEXT:
The 65-kDa isoform of glutamic acid decarboxylase ([GAD.sub.65]) has been implicated in autoimmune diabetes in NOD mice, but the role of the 67-kDa GAD isoform ([GAD.sub.67]) is less clear. We found that immunization of 4-week-old NOD mice with purified recombinant mouse [GAD.sub.67] prevented or significantly delayed the onset of diabetes. To further explore this phenomenon, we characterized anti-[GAD.sub.67] immune responses to naive and GAD-immunized NOD mice. Anti-[GAD.sub.67] antibodies titers were relatively low in naive mice at all ages, but a single immunization with [GAD.sub.67] at 4 weeks induced high titers of anti-GAD antibodies by 6 weeks of age. In both 4-week-old and diabetic NOD mice,

there were significant endogenous T-cell proliferative responses against purified recombinant mouse [GAD.sub.67]. These T-cell proliferative responses were blocked by anti-I-[A.sup.NOD] and anti-CD4 antibodies. To characterize the anti-GAD T-cell responses in the NOD mice, we established T-cells lines and T-cell clones which recognized [GAD.sub.67], and we used recombinant subfragments of GAD to localize the predominant T-cell epitopes in [GAD.sub.67]. T-cells from naive NOD mice proliferated in response to all GAD subfragments, whereas T-cells from diabetic mice responded primarily to the COOH-terminal 83 amino acids of [GAD.sub.67]. These results suggest that [GAD.sub.67] is an autoantigen in IDDM and immunization of prediabetic NOD mice with [GAD.sub.67] can prevent the onset of diabetes. Diabetes 43:1494-1499, 1994

Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease that results from the destruction of insulin-producing [Beta]-cells in the islets of Langerhans[1]. This destruction is manifested by mononuclear cell infiltrates and a chronic inflammatory process in the islets of genetically predisposed individuals[2]. The selective destruction of [Beta]-cells is probably associated with autoantigens that for some unknown reason become the target for immune recognition[3]. Antibodies to islet-associated antigens are present before the onset of IDDM; they include anti-islet cell antibodies, anti-insulin autoantibodies[2,3], antibodies to carboxypeptidase-H[4], antibodies to a 69-kDa protein possibly related to bovine serum albumin[5], and antibodies to a 64-kDa islet protein[6,7]. In humans, this 64-kDa autoantigen has been shown to be immunologically indistinguishable from the 65-kDa isoform of glutamic acid decarboxylase ([GAD.sub.65])[6,7].

GAD catalyzes the synthesis of the inhibitory neurotransmitter [gamma]-aminobutyric acid (GABA), and in the mammalian central nervous system it exists in two isomeric forms, [GAD.sub.65] and [GAD.sub.67][8]. Whereas rat and human pancreatic islets express [GAD.sub.65] predominantly or exclusively[9,10], mouse islets express both [GAD.sub.65] and [GAD.sub.67], and [GAD.sub.67] appears to predominate[11]. In human diabetic patients, if anti-GAD autoantibodies are present, they appear to be primarily against the [GAD.sub.65] isoform[7,10]. Autoantibodies to GAD have also been reported in BB rats and in NOD mice[12,13], although the GAD isoforms that are predominantly recognized in these animal models remain to be determined.

Both the [GAD.sub.65] and [GAD.sub.67] cDNAs have been cloned from rat[14] and human[15] brain, and the [GAD.sub.65] cDNAs have also been cloned from rat[16] and human[17] islets. The cDNA encoding mouse brain [GAD.sub.67] has been known for some time[18], ana more recently mouse [GAD.sub.65] has also been characterized[19]. GAD from cat brain[20] and Drosophila[21] have also been cloned. The availability of these cloned genes has made it possible to produce relatively large quantities of recombinant GAD in Escherichia coli or other expression systems. However, despite the fact that [GAD.sub.67] is the predominant isoform found in mouse islets, most immunological characterization in NOD mice has thus far focused on [GAD.sub.65]. In this study we characterize the endogenous and induced immune responses against [GAD.sub.67] in NOD mice.

RESEARCH DESIGN AND METHODS

NOD/Alt mice were obtained from the University of Alberta breeding colony, where the incidence of diabetes in female NOD mice is 80% by 20 weeks of age.

Antibodies. For antibody-blocking experiments, anti-CD4 (GK1.5) hybridoma supernatants were purified by ammonium sulfate precipitation (50%); dilutions were made from a 250 [mu]g/ml stock of salt-cut dialyzed protein. Anti-I-[A.sup.NOD] antibody (10.2.16) was added as ascites fluid at the dilutions indicated[22].

Cloning and expression of recombinant GAD and GAD subfragments. The cDNA clone 1A1, which encodes mouse [GAD.sub.67], was obtained from R. Greenspan (Roche Institute of Molecular Biology, Nutley, NJ). DNA sequencing of the 3' end of the 1A1 clone showed that the sequence was slightly different from that originally reported by Katarova et al.[18]. The specific changes were: insertion of a single G after nucleotide 1775, substitution of T for A at 1777, substitution of A for T at 1778, substitution of A for T at 1837, substitution of T for C at 1862, and substitution of T for C at 1863 (nucleotide numbering is the sanie as in Katarova et al.). These changes cause a shift in the reading frame and indicate that the true COOH terminus of mouse [GAD.sub.67] is different from that originally reported[18], but highly similar in sequence to that of [GAD.sub.65] and [GAD.sub.67] from a number of species[17].

The expression plasmid pT7-7 was obtained from S. Tabor, Harvard University (Cambridge, MA). The DNA sequence of the pT7-7 polylinker was determined to be [5'CATATGGCTAGAATTCGCGCCCGGGGATC CTCTAGAGTCGACCTGCAGCCCAAGCTTATCGATGATAAGCTGTCAA ACATGA-3'!, with translation beginning at the 5' most ATG. We constructed the expression plasmid pT7-7His6 by adding the sequence [5'-CATATGCACCACCACCACCACCACCTGGTTCCGCGTGGTTCCGGA ATTC-3'! between the Nde I and Eco RI sites of the polylinker, using standard cloning methods[23]. The cDNA clone 1A1 was digested with Eco RI, and

5 ng of this material was amplified through 25 cycles of polymerase chain reaction in the presence of the primers 5'ATATATGA ATTCGCGCCATGGCATCTTCCACTCCTTC3' (5' primer) and 5'CT CTCTAAGCTTTTACAGATCCTGACCCAACCTCTC3'(3' primer). The resulting

1,800-base pair fragment was gel-purified, digested with Eco RI and Hin dIII, and ligated into pT7-7His6, which had been previously digested with the same enzymes. The protein expressed by this construct is referred to as MG1H. It is identical to mouse [GAD.sub.67], except that the sequence MHHHHHHLVPRGSGIRA has been added to the [NH.sub.2]-terminus (Fig. 5). The six histidine residues followed by a thrombin cleavage site allow for affinity purification over a nickelchelating column under denaturing conditions. Recombinant [GAD.sub.67] subfragments were engineered using a similar polymerase chain reaction strategy.

To express the recombinant proteins we transfected the corresponding plasmid into E. coli BL21/DE3[24] and grew several fresh colonies in individual small-scale cultures to test for protein expression. For larger scale expression, 1-liter cultures in 2 x yeast tryptone[23], 100 [mu]g/ml ampicillin, 0.2 mmol/l pyridoxal phosphate were grown in an air shaker at 37[degrees]C to an [OD.sub.600] of 0.6-0.8, and then induced with 0.4 mmol/l isopropyl-1-thio-[Beta]-D-galactopyranoside and grown for a further 3-4 h. Cells were collected by centrifugation (2,200 g, 4[degrees]C, 30 min), and the cell pellets were drained and resuspended in TPB (10 mmol/l Tris-HCl and 100 mmol/l phosphate buffer, pH 8.0; [tilde]20 ml/l of original culture). RNase A (2 [mu]g/ml), DNase (4 [mu]g/ml), and phenylmethylsulfonyl fluoride (1 mmol/l) (all reagents from Sigma, St. Louis, MO) were added and the cells were opened by passing them twice through a French press (16,000 psi). The bacterial extracts were centrifuged at 5,000 g at 4[degrees]C for 30 min to pellet the insoluble inclusion bodies, and peuets were resuspended in TPB (pH 8.0) and 6 mol/l guanidine HCl.

The recombinant proteins were purified by affinity chromatography over a nickel-chelating column and elution in 8 mol/l urea and TPB at low pH as described by Hochuli et al.[25]. The recombinant GAD proteins eluted at pH 5.0 and 4.5. These eluates were collected in fractions, and each fraction was analyzed by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE). Fractions containing the recombinant protein were

pooled and then dialyzed at 4[degrees]C against SDS-PAGE running buffer (0.1% SDS)[23] for 24 h, SDS-PAGE running buffer (0.01% SDS) for 24 h, 4 mmol/l HEPES (pH 7.4) for 24 h, and finally 4 mmol/l HEPES (pH 7.4), 0.05 mmol/l pyridoxal phosphate for 24 h. The dialyzed material was lyophilized and stored as dry powder at -70[degrees]C. For immunological assays or immunizations, the lyophilized material was resuspended in phosphate-buffered saline (PBS) or RPMI-1640 at 1-2 mg/ml protein, sterilized by filtration (0.22 [mu]m), and stored at -20[degrees]C.

Immunization and monitoring for diabetes onset. Fifty microliters of purified recombinant [GAD.sub.67] (2 mg/ml in PBS) was emulsified with an equal volume of incomplete Freund's adjuvant (IFA) (GIBCO/BRL, Grand Island, NY), and the entire 100-[mu]l mixture was injected intraperitoneally into 4-week-old female NOD mice. Control mice received 50 [mu]l of IFA emulsified with 50 [mu]l of PBS alone. All mice were monitored biweekly for urine glucose using TES-TAPE I (Lilly, Indianapolis, IN). Once the urine tested positive for glucose, blood glucose levels were monitored daily using Glucoscan 2000 test strips (Lifescan, Milpitas, CA). Mice were killed when blood glucose levels rose above 16.7 mmol/l on 2 consecutive days.

Measurement of anti-GAD antibodies by enzyme-linked immunosorbent assay (ELISA). Flat-bottomed 96-well plates (Pro-Bind; Falcon, Oxnard, CA) were coated with recombinant purified [GAD.sub.67] (10 Kg protein/ird in 0.2 mol/l Tris-HCl, pH 7.2; 50 [mu]l/well) by incubating overnight at 4[degrees]C. The ELISA assay was performed using standard methods, and results are presented as absorbance at 405 nm, recorded by using a Molecular Devices [UV.sub.max] kinetic microplate reader.

T-cell proliferation assays. Single cell suspensions of cells were obtained from the spleen or lymph nodes as described[26], and erythrocytes were lysed by incubation for 2 min at 18[degrees]C in a solution of Tris-HCl (170 mmol/l), pH 7.2) and [NH.sub.4]Cl (0.83% wt/vol). The cells were washed, resuspended in complete RPMI media (RPMI-1640, 100 [mu]g/ml gentamycin, 10 mmol/l HEPES, [10.sup.-5] mmol/l 2-mercaptoethanol, and 10% fetal calf serum), and a nylon wool column used to enrich for T-lymphocytes as described[27]. The column and cells were incubated 1 h at 37[degrees]C, and nonadherent cells were collected by washing the column with several volumes of complete RPMI (prewarmed to 37[degrees]C); 3,000 rad irradiated spleen cells were used as antigen-presenting cells (APCs). T-cell proliferation assays were done in flat-bottomed 96-well plates using complete RPMI media (200 [mu]l/well) with varying amounts of antigen, 2 x [10.sup.5] bulk T-lymphocytes, and 4-5 x [10.sup.5] APCs added per well. The cultures were incubated for 80 h, then pulsed with [[methyl-.sup.3]H] thymidine (1 [mu]Ci/well; Du Pont-NEN, Boston, MA), harvested onto glass fiber filters 16 h later, and counted in a scintillation counter.

GAD reactive T-cell lines and clones. To establish T-cell lines, NOD mice were immunized in the hind footpad with 100 [mu]l mouse [GAD.sub.67] in IFA (1.0 mg/ml [GAD.sub.67] in PBS emulsified with an equal volume of IFA). Ten days later the draining popliteal lymph node was removed, and nylon wool-enriched T-cells were prepared and plated out in 96-well flat-bottomed plates (4 x [10.sup.5] T-cells/ml; 200 [mu]l/well). Cultures were stimulated with mouse [GAD.sub.67] (20 [mu]g/ml) in the presence of 3,000 rad irradiated syngeneic spleen cells (1 x [10.sup.6] cells/well). After 5 days, cells were transferred to 24-well plates and incubation was continued in the presence of a 1:100 dilution of rat interleukin-2 (IL-2) (natural rat interleukin-2, partialy purified, from Collaborative Research, Bedford, MA). Seven to 10 days later, live cells were purified by centrifugation over Lympholyte-M (Cederlane, Hornby, Ontario, Canada), and antigen specificity was tested using the standard proliferation assay described above (20 [mu]g/ml [GAD.sub.67]). Antigen-specific cell lines

were expanded using alternating cycles of stimulation with [GAD.sub.67] and irradiated APCs (5 days of culture with 20 [mu]g/ml GAD67 and 1 x [10.sup.6] APCs/well), followed by stimulation with rat IL-2 (10 days of culture with 1:100 dilution).

T-cell clones were established from the antigen-specific [GAD.sub.67]-reactive T-cell lines by the limiting dilution method. Cells were plated in 96-well plates (0.3 cells/well) in the presence of irradiated syngeneic spleen cells (5 x [10.sub.5] cells/well), [GAD.sub.67] (20 [mu]g/ml), and rat IL-2 (1:100 dilution in RPMI-1640). Ten to 15 days later, cloned T-cells were transferred into 24-well plates and expanded using alternating cycles of stimulation with [GAD.sub.67] and irradiated APCs (5 days of culture with 20 [mu]g/ml [GAD.sub.67] and 5 x [10.sup.5] APCs/well), followed by stimulation with rat IL-2 (10 days of culture with 1:100 dilution). To demonstrate antigen specificity, cloned 7-cells (1 x [10.sup.4] cells/well) were incubated with irradiated syngeneic spleen cells (5 x [10.sup.5] cells/well) and [GAD.sub.67] (20 [mug/ml), and proliferation was measured after 96 h.

RESULTS

SDS-PAGE analysis of purified GAD antigens. Recombinant mouse [GAD.sub.67] was purified as described under METHODS,

5 [mu]g of purified protein was separated on SDS-PAGE, and the gel was stained with Coomassie blue. A single predominant band of the expected size was observed (Fig. 1).

Administration of mouse GAD67 prevents NOD mice from developing spontaneous diabetes. To detemine what effect the deliberate induction of anti-[GAD.sub.67] immune responses would have on the onset of diabetes, we immunized 4-week-old female NOD mice with purified [GAD.sub.67] in IFA and followed them for the onset of hyperglycemia. In preliminary experiments (data not shown), five IFA-immunized control mice became diabetic by 20 weeks, whereas five [GAD.sub.67]-immunized mice remained diabetes free for >35 weeks. This experiment was repeated with 10 to 15 mice/group, and the results are shown in Fig. 2. In this case, three of the IFA-immunized mice and all of the [GAD.sub.67]-immunized mice remained diabetes free for >35 weeks.

A single immunization with mouse [GAD.sub.67] induces anti-GAD antibodies. Using purified recombinant mouse [GAD.sub.67], we established an ELISA that could be used to measure titers of anti-mouse GAD antibodies. We found minimal levels of anti-GAD antibodies in 6-week-old naive NOD mice, and titers were essentially the same in diabetic mice. In contrast, in mice immunized with mouse [GAD.sub.67] at 4 weeks of age, antibody titers were increased at least 30-fold by 6 weeks of age (Fig. 3).

NOD T-lymphocytes proliferate in response to mouse [GAD.sub.67], and this proliferation is blocked by anti-I-A and anti-CD4 antibodies. T-lymphocytes were purified from the lymph nodes of prediabetic (6-week-old) and diabetic female NOD mice, mixed with irradiated spleen cells as APCs, and cultured in the presence of recombinant mouse [GAD.sub.67]. At both ages, a strong anti-[GAD.sub.67] Proliferative response was seen, and in both cases this proliferation could be blocked by either anti-I-[A.sup.NOD] or anti-CD4 antibodies (Fig. 4).

NOD T-cell lines and clones that recognize recombinant mouse [GAD.sub.67]. We raised T-cell lines by stimulating NOD T-lymphocytes repeatedly with purified recombinant mouse [GAD.sub.67] in the presence of APCs. Two independent T-cell lines, ML1 and ML3, were established. Both showed strong proliferative responses to mouse [GAD.sub.67] (Table 1). Using the same antigen preparation on limiting dilution cultures, we raised two GAD-reactive T-cell clones, M3.3 and M3.5 (Table 2). These clones proliferate in response to recombinant mouse [GAD.sub.67] and APCs but do not show significant proliferative response to an unrelated recombinant

malaria antigen preparation (PfsY-C1), which was expressed and purified in an identical fashion as the recombinant [GAD.sub.67].

[TABULAR DATA OMITTED]

T-cell proliferative responses to recombinant subfragments of mouse [GAD.sub.67]. To better define the region of mouse [GAD.sub.67] that is recognized by NOD T-lymphocytes, we expressed and purified the subfragments of the protein shown in Fig. 5. Bulk splenic T-cells from 6-week-old mice appeared to recognize all four [GAD.sub.67] subfragments, although subfragments 2 and 5 give the strongest proliferative response (Fig. 6A). In contrast, splenic T-cells from diabetic mice appear to have a much stronger proliferative response to subfragment 5, and the proliferative responses to the other subfragments are correspondingly diminished.

DISCUSSION

Since [GAD.sub.67] appears to be the predominant GAD isoform expressed in mouse islets (11), we assumed that it would be a major target of the autoimmune response in NOD mice. This assumption is supported by the work of Tisch et al.[28], who showed that prediabetic NOD mice have T-cell responses against both mouse GAD isoforms. Kaufman et al.[29] have shown that immunization of young NOD mice with human [GAD.sub.65], can prevent diabetes, but we were interested to know if mouse [GAD.sub.67] would have a similar effect. If, for example, [GAD.sub.67] failed to protect, it would suggest a relatively unique role for [GAD.sub.65] in the autoimmune process. Our preliminary results suggested that immunization with [GAD.sub.67] also has a protective effect, and subsequent experiments using a larger number of animals confirmed this observation. This implicates [GAD.sub.67] in the autoimmune process in NOD mice and led us to investigate the nature of the antibody and T-cell responses against [GAD.sub.67] in the naive and GAD-immunized animals.

Naive NOD mice had minimal titers of anti-[GAD.sub.67] antibodies, and these increased only slightly as the niice aged. In contrast, but perhaps not unexpectedly, in mice that were inununized with a single dose of mouse [GAD.sub.67] in IFA, the titers of anti-mouse GAD67 antibodies rose significantly within a few weeks (Fig. 2).

In contrast to antibody responses, both 4-week-old and diabetic NOD mice had significant endogenous T-cell proliferative responses against purified recombinant mouse [GAD.sub.67]. To further characterize the proliferating cell populations, we incubated purified T-cells, antigen, and irradiated APCs in the presence of two different blocking monoclonal antibodies (Fig. 4). Inhibition by the anti-I-[A.sup.NOD] monoclonal antibody suggests that presentation of the GAD antigen via class II molecules is required to stimulate the majority of the [GAD.sub.67]-reactive T-cells. Furthermore, many of the proliferating T-cells are [CD4.sup.+], because the anti-CD4 appears to consistently reduce prouferation to roughly the same levels as seen with the anti-class H antibody.

Although the [GAD.sub.67] used in our T-cell proliferation assays was highly purified (Fig. 1), the antigen preparation could potentially contain additional mitogenic agents. Such agents would stimulate lymphocyte proliferation (T- and/or B-lymphocytes) in a nonspecific manner that would be independent of antigen presentation. However, the fact that T-cells from other strains of mice did not proliferate in response to the GAD preparation (data not shown), together with the observation that the NOD T-cell proliferative responses are significantly blocked by anti-I-[A.sup.NOD], supports the idea that this response is antigen-specific and that it requires the presentation of GAD peptides by NOD class II molecules.

To further characterize the anti-[GAD.sub.67] T-cell response, we have developed GAD specific T-cell lines and clones (Tables 1 and 2). The

fact that such lines and clones can be established provides additional evidence that T-cells which recognize [GAD.sub.67] exist within the NOD inimune system. These [GAD.sub.67] reactive T-cell lines and clones can now be used to map T-cell epitopes within [GAD.sub.67].

Rather than mouse [GAD.sub.67], it is possible that some contaminating bacterial protein in the antigen preparation might be presented on NOD class II molecules and induce proliferation of the T-cell clones M3.3 and M3.5. To exclude this possibility, we tested the clones for proliferative response to an unrelated recombinant malarial antigen, PfsY-Cl. This malaria antigen has the same [NH.sub.2]-terminal Met[(His).sub.6] and thrombin cleavage site as the recombinant mouse [GAD.sub.67] molecules (see Fig. 5 legend), and it was expressed in the same bacterial host and purified over a nickel-chelating column using identical conditions as for the recombinant GAD antigen preparations. Thus, any nonspecific bacterial contaminants that are present in the recombinant [GAD.sub.67] would also be present in the PfsY-C1 antigen preparation. However, the malaria antigen did not stimulate proliferation of the [GAD.sub.67] reactive T-cell lines (data not shown) or clones (Table 2).

[TABULAR DATA OMITTED]

To delineate the predominant T-cell epitopes in [GAD.sub.67], we made and purified subfragments of mouse [GAD.sub.67] (Fig. 5) and used the various purified polypeptides in a proliferation assay with nylon wool-enriched splenic T-cells from 6-week-old and diabetic NOD ntice (Flg. 6). These results suggest that whereas 6-week-old mice see a variety of epitopes on [GAD.sub.67], as the animals progress to diabetes the immune response appears to be increasingly limited to fragment 5, which contains residues 400-585 of [GAD.sub.67]. However, because the same cells do not respond to fragment 4, which includes residues 300-502, this would suggest that the major T-cell epitope is limited to the COOH-terminal 83 amino acids of [GAD.sub.67].

A limited number of specific peptides derived from the human [GAD.sub.65] protein have recently been shown to stimulate the proliferation of splenic T-cells from young prediabetic NOD mice[29], and these peptides are thought to embody the predominant and earliest T-cell determinants of [GAD.sub.65] recognized by the NOD immune system. These peptides come largely from near the COOH terminus of human [GAD.sub.65], and a highly similar sequence occurs in the COOH-terminal region of mouse [GAD.sub.67], with the corresponding peptide elements found entirely within the COOH-terminal 83 amino acids of [GAD.sub.67]. However, the findings of Kaufman et al.[29] using the set of overlapping human [GAD.sub.65] peptides suggest that T-cells from young NOD mice initially recognize a limited region of [GAD.sub.65] and that as the autoimmune response progresses, the NOD inimune system recognizes an increasing number of different peptide elements derived from [GAD.sub.65]. In contrast, our results suggest that as the autoimmune response progresses, an increasing proportion of the GAD-reactive T-cells recognize a limited subsegment of [GAD.sub.67], which lies within the COOH-terminal 83 amino acids of the molecule.

Given that immunization with mouse [GAD.sub.67] appeared to delay the onset of diabetes in NOD mice, it is interesting to consider exactly how the existing endogenous anti-GAD immune response may have been altered by the immunization. It is likely that the subset of T-cells that are induced by GAD immunization are of T-helper 2 (TH2) type and these cells block the potentially autoreactive T-helper 1 (TH1) type cells. This may be similar to what might happen when NOD mice are protected from IDDM by immunostimulation with adjuvants such as CFA[30]. In terms of subclasses of T-cell responses[31], we have not yet carried out a detailed analysis of the differences between the GAD-reactive T-cells from our GAD-immunized (i.e., protected) mice and our nonimmunized (i.e., susceptible) mice. From

our existing data we can say that the anti-GAD antibody titers are much higher in the immunized mice than in the nonimmunized animals, and this may reflect a shift in anti-GAD T-cell immune responses toward a TH2-like response in the immunized group. This idea is at least consistent with the finding that in normal (i.e., unimmunized, prediabetic) NOD mice, the endogenous anti-mouse GAD T-cell response is essentially TH1-like[29]. Our results suggest potential immunotherapy of autoimmune diseases such as IDDM by immunization with relevant autoantigens that could alter the ratio of subset T-helper-cell subset.

REFERENCES

[1.] Cooke A: An overview on possible mechanisnis of destruction of the insulin-producing beta cell. Curr Topics Microbiol Immunol 164:125-142, 1990 [2.] Castano L, Eisenbarth GS: Type-I diabetes: a chronic autoimmune disease of human, mouse, and rat. Annu Rev Immunol 8:647-679, 1990 [3.] Harrison LC: Islet cell antigens in insulin-dependent diabetes: Pandora's box revisited. Immunol Today 13:348-352, 1992 [4.] Castano L, Russo E, Zhou L, Lipes MA, Eisenbarth GS: Identification and cloning of a granule autoantigen (carboxypeptidase-H) associated with type I diabetes. J Clin Endrocrinol Metab 73:1197-1201, 1991 [5.] Karjalainen J, Martin JM, Knip M, Ionen J, Robinson BH, Savilahti E, Akerblom HK, Dosch H: A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus. N Engl J Med 327:302-307, 1992 [6.] Baekkeskov S, Warnock G, Christie M, Rajotte RV, Larsen PM, Fey S: Revelation of specificity of 64K autoantibodies in IDDM serums by high-resolution 2-D gel electrophoresis: unambiguous identification of 64K target antigen. Diabetes 38:1133-1141, 1989 [7.] Baekkeskov S, Aanstoot HJ, Christgau S: Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Natum 347:151-156, 1990 (Published erratum appears in Nature 347:782, 1990) [8.] Erlander MG, Tobin AJ: The structural and functional heterogeneity of glutamic acid decarboxylase: a review. Neurochem Res 16:215-226, 1991 [9.] Karlsen AE, Hagopian WA, Petersen JS, Boel E, Dyrberg T, Grunin CE, Michelsen BK, Madsen OD, Lernmark A: Recombinant glutamic acid decarboxylase (representing the single isoform expressed in human islets) detects IDDM-associated 64,000-[M.sub.r] autoantibodies. Diabetes 41: 1355-1359,1992 [10.] Hagopian WA, Michelsen B, Karlsen AE, Larsen F, Moody A, Grubin DC, Rowe R, Petersen J, McEvoy R, Lernmark A: Autoantibodies in IDDM primarily recognize the 65,000-[M.sub.r] rather than the 67,000-[M.sub.r] isoform of glutamic acid decarboxylase. Diabetes 42:631-636, 1993 [11.] Kim J, Richter W, Aanstoot H-J, Shi Y, Fu Q, Rojotte R, Warnock G, Baekkeskov S: Differential expression of [GAD.sub.65] and [GAD.sub.7] in pancreatic islets of man, rat, and mouse. Diabetes 42:1799-1808, 1993 [12.] Baekkeskov S, Dyrberg T, Lernmark A: Autoantibodies to a 64-kilodalton islet cell protein precede the onset of spontaneous diabetes in the BB rat. Science 224:1348-1350, 1984 [13.] Atkinson MA, Maclaren NK: Autoantibodies in nonobese diabetic mice immunoprecipitate 64,000-[M.sub.r] islet antigen. Diabetes 37:1587-1590, 1988 [14.] Erlander MG, Tilakaratne NJ, Feldblum S, Patel N, Tobin AJ: Two genes encode distinct glutamate decarboxylases. Neuron 7:91-100, 1991 [15.] Bu D, Erlander MG, Hitz BC, Tilakaratne NJ, Kaufman DL, Wagner-McPherson CB, Evans GA, Tobin AJ: Two human glutamate decarboxylases, 65-kDa GAD and 67-kDa GAD, are each encoded by a single gene. Proc Natl Acad Sci USA 89:2115-2119, 1992 [16.] Michelsen BK, Petersen JS, Boel E, Moldrup A, Dyrberg T, Madsen OD: Cloning, characterization, and autoimmune recognition of rat islet glutamic acid decarboxylase in insulin-dependent diabetes mellitus. Proc Natl Acad Sci USA 88:8754-8758, 1991 [17.] Karlsen AE, Hagopian WA, Grubin CE, Dube S, Disteche CM, Adler DA, Barmeier H, Mathewes S, Grant FJ, Foster D, Lernmark A: Cloning and primary structure of a human islet isoform of glutamic acid decarboxylase from chromosome 10. Proc Natl

Acad Sci USA 88:8337-8341, 1991 [18.] Katarova Z, Szabo G, Mugnaini E, Greenspan RJ: Molecular identification of the 62 kd form of glutamic acid decarboxylase from the mouse. Eur J Neurosci 2:190-202, 1990 [19.] Lee DS, Tian J, Phan T, Kaufman DL: Cloning and sequence analysis of a murine cDNA encoding glutamate decarboxylase (GAD65). Biochim Biophys Acta 1216:157-160, 1993 [20.] Kobayashi Y, Kaufman DL, Tobin AJ: Glutamic acid decarboxylase cDNA nucleotide sequence encoding an enzymatically active fusion protein. J Neurosci 7:2768-2772, 1987 [21.] Jackson FR, Newby LM, Kulkarni SJ: Drosophila GABAergic systems sequence and expression of glutamic acid decarboxylase. J Neurochem 54:1068-1078, 1990 [22.] Singh B, Dillon T, Fraga E, Lauzon J: Role of the first external domain of I-A beta chain m mimune responses and diabetes in non-obese diabetic (NOD) mice. J Autoimmun 3:507-521, 1990 [23.] Sambrook J, Fritsch EF, Maniatis T: Molecular Cloning: A Laboratory Manual. 2nd ed. Cold Spring Harbor, NY, Cold Spring Harbor Press, 1989 [24.] Studier FW, Rosenberg AH, Dunn JJ, Dubendorff JW: Use of T7 RNA polymerase to direct expression of cloned genes. Methods Enzymol 185:60-89, 1990 [25.] Hochuli E, Bannworth W, Dobeli H, Gentz R, Stuber D: Genetic approach to facilitate purification of recombinant proteins with a novel metal chelate adsorbent Bio/Technology 6:1321-1325, 1988 [26.] Fotedar A, Boyer M, Smart W, Widtman J, Fraga E, Singh B: Fine specificity of antigen recognition by T cell hybridoma clones specific for poly-18. a synthetic polypeptide antigen of defined sequence and conformation. J Immunol 135:3028-3033, 1985 [27.] Fotedar A, Smart W, Boyer M, Dillon T, Fraga E, Lauzon J, Shevach EM, Singh B: Characterization of agretopes and epitopes involved in the presentation of beef insulin to T cells. Mol Immunol 27:603-611, 1990 [28.] Tisch R, Yang X-D, Singer SM, Liblau RS, Fugger L, McDevin HO: Immune response to glutamic acid decarboxylase correlates with insulitis in non-obese diabetic mice. Nature 366:72-75, 1993 [29.] Kaufman DL, Clare-Salzler M, Tian J, Forstuber T, Ting GS, Robinson P, Atkinson MA, Sercarz EE, Tobin AJ, Lehmann PV: Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. Nature 366:69-72, 1993 [30.] Qin HY, Sadelain MWJ, Hitchon C, Lauzon J, Singh B: Complete Freund's adjuvant-induced T cells prevent the development and adoptive transfer of diabetes in nonobese diabetic mice. J Immunol 150:2072-2080, 1993 [31.] Powrie F, Coffman RL- Cytokine regulation of T-cell function: potential for therapeutic intervention. Immunol Today 14:270-274, 1993
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Oral tolerance: Immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens

Weiner H.L.; Friedman A.; Miller A.; Khoury S.J.; Al-Sabbagh A.; Santos L.; Sayegh M.; Nussenblatt R.B.; Trentham D.E.; Hafler D.A.

Center for Neurologic Diseases, Brigham and Women's Hospital, Beth Israel Hosp./Harvard Med. Sch., Boston, MA 02115 USA

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Oral tolerance is a long recognized method to induce peripheral immune tolerance. The primary mechanisms by which orally administered antigen induces tolerance are via the generation of active suppression or clonal anergy. Low doses of orally administered antigen favor active suppression whereas higher doses favor clonal anergy. The regulatory cells that mediate active suppression act via the secretion of suppressive cytokines such as TGFbeta and IL-4 after being triggered by the oral tolerogen. Furthermore, antigen that stimulates the gut-associated lymphoid tissue preferentially generates a Th2 type response. Because the regulatory cells generated following oral tolerization are triggered in an antigen-specific fashion but suppress in an antigen nonspecific fashion, they mediate 'bystander suppression' when they encounter the fed autoantigen at the target organ. Thus it may not be necessary to identify the target autoantigen to suppress an organ-specific autoimmune disease via oral tolerance; it is necessary only to administer orally a protein capable of inducing regulatory cells that secrete suppressive cytokines. Orally administered autoantigens suppress several experimental autoimmune models in a disease- and antigen-specific fashion; the diseases include experimental autoimmune encephalomyelitis (EAE), uveitis, and myasthenia, collagen- and adjuvant-induced arthritis, and diabetes in the NOD mouse. In addition, orally administered alloantigen suppresses alloreactivity and prolongs graft survival. Initial clinical trials of oral tolerance in multiple sclerosis, rheumatoid arthritis, and uveitis have demonstrated positive clinical effects with no apparent toxicity and decreases in T cell autoreactivity.

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DRUG DESCRIPTORS:
*transforming growth factor beta--endogenous compound--ec; *autoantigen --pharmacology--pd; *autoantigen--pharmacokinetics--pk; *autoantigen--drug therapy--dt; *autoantigen--drug administration--ad; *myelin basic protein --endogenous compound--ec
MEDICAL DESCRIPTORS:
*anergy (immunopathology); *immunological tolerance; *autoimmunity --etiology--et; *autoimmunity--therapy--th; *autoimmunity--drug therapy--dt ; *intestine lymphatic tissue; *allergic encephalomyelitis--etiology--et; * allergic encephalomyelitis--therapy--th; *immunomodulation
antigen presentation; human; rat; oral drug administration; intravenous drug administration; priority journal; review
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12/9/14 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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9586511 EMBASE No: 95150201
Tolerogenic forms of auto-antigens and cytokines in the induction of resistance to experimental allergic encephalomyelitis
Santambrogio L.; Crisi G.M.; Leu J.; Hochwald G.M.; Ryan T.; Thorbecke G.J.

Department of Pathology, New York University Medical Center, 550 First Avenue, New York, NY 10016 USA
Journal of Neuroimmunology (Netherlands) , 1995, 58/2 (211-222) CODEN: JNRID ISSN: 0165-5728
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 008; 026
Resistance to experimental allergic encephalomyelitis (EAE) induction by homogenized myelin (MSCH) in complete Freund's adjuvant (CFA) and pertussigen (P) in SJL mice was seen 1 week after intravenous injection of PLP 139-151 coupled to spleen cells (PLP-ECDT-SP). Although this resistance could be transferred by spleen cells enriched for CD8+ T cells and thus had a component of immunoregulatory T cells, it was primarily due to anergy. as it was reversible by four daily injections of interleukin 2 starting 3 days after the PLP-ECDI-SP. Earlier treatment with IL-2 did not reverse the tolerance. In view of the known higher sensitivity to anergy induction of Th1 than of Th2 cells, a change in the cytokine balance in the response to MSCH + CFA after anergy induction might be responsible for the resistance to EAE induction. The effect of treatment with cytokines alone on induction of EAE was therefore also determined. Short-term (1-2 weeks) daily pretreatment with IL-2 (4000 U) or TGF-beta2 (1 microg) somewhat decreased the susceptibility to subsequent EAE induction, but IL-4 (5 microg), IL-10 (5 microg) or IL-12 (50-200 ng) had no effect under those conditions, even if low doses of PLP were injected simultaneously. Daily injections of IL-4 over an 8-week period prior to immunization, however, significantly lowered the incidence of EAE. Simultaneous injections of IFN-gamma (2000 U/day) completely abolished this effect of IL-4. The effect of these cytokines administered immediately after the immunization with MSCH + CFA + P was also examined. As shown earlier, TGF-beta2 (100-1000 ng/day) caused a marked protection when it was given intraperitoneally on days 5-9 after injection of MSCH + CFA. IL-4 (5 ng/day), in contrast, was very protective when administered on days 0-4 and less so when given on days 5-9 or even on days 0-12. IL-10 (1 microg/day) was not protective under these conditions and IL-12 50 ng/day) significantly increased the severity and mortality of EAE when given on days 0-4 after MSCH + CFA.

EMTAGS:
Nonhuman 0777; Mouse 0727; Mammal 0738; Controlled study 0197; Animal experiment 0112; Animal model 0106; Biological models 0502; Female 0042; Intravenous drug administration 0182; Priority journal 0007; Article 0060; Nervous system 0910; Peripheral nervous system 0913
DRUG DESCRIPTORS:
*myelin; *freund adjuvant; *pertussis toxin; *transforming growth factor beta; *gamma interferon
interleukin 2; interleukin 10; interleukin 12; interleukin 4
MEDICAL DESCRIPTORS:
*allergic encephalomyelitis; *autoimmunity; *disease predisposition
nonhuman; mouse; controlled study; animal experiment; animal model; female; intravenous drug administration; priority journal; article
EMCLAS DRUG CODES:
03700000000

CAS REGISTRY NO.: 9007-81-2; 70323-44-3; 82115-62-6; 85898-30-2; 138415-13-1

12/9/13 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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9749569 EMBASE No: 95303400

Self-antigen-induced Th2 responses in experimental allergic encephalomyelitis (EAE)-resistant mice: Th2-mediated suppression of autoimmune disease

Cua D.J.; Hinton D.R.; Stohlman S.A.
MHC 142, USC School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033 USA

Journal of Immunology (USA) , 1995, 155/8 (4052-4059) CODEN: JOIMA
ISSN: 0022-1767
LANGUAGES: English SUMMARY LANGUAGES: English
SUBFILES: 008; 026

Immunization of a limited number of rodent strains with central nervous system-derived Ags induces experimental allergic encephalomyelitis (EAE). In contrast to susceptible female SJL mice, age-matched males are resistant to actively induced EAE. The ability of immunization with neuroAg to induce Ag- specific T cell activation in resistant male mice was examined. Ag-specific T cell proliferation was found following immunization of both male and female SJL mice. Draining lymph node cytokine mRNA patterns demonstrated that immunization of EAE-resistant male mice resulted in a Th2-type pattern. By contrast, immunization of EAE-susceptible female mice resulted in a Th1-type pattern. Priming of Th1- and Th2-type responses was confirmed by analysis of cytokines secreted following Ag-specific proliferation. In contrast to the transfer of myelin basic protein (MBP)-specific Th1-type T cells derived from female mice, which induced acute and relapse EAE, transfer of MBP-specific Th2-type T cells derived from male mice resulted in no clinical or histologic evidence of EAE. A mixture of MBP-specific Th1 and Th2 type cells was transferred to naive recipients to determine if the neuroAg-specific Th2- type cells exerted a regulatory influence on EAE. Acute disease was partially eliminated and relapses were completely eliminated in these recipients. Analysis of spinal cords showed the presence of both Th1 and Th2 cytokine mRNAs. These data are consistent with both the ability of Th2-type cells to suppress autoimmunity and a homeostatic mechanism of T cell regulation based on the cross-regulation of Th1 and Th2 cells in the maintenance of peripheral tolerance.

/

BRAND NAME/MANUFACTURER NAME: USA sigma

EMTAGS:
Etiology 0135; Prevention 0165; Therapy 0160; Blood and hemopoietic system 0927; Lymphatic system 0929; Nonhuman 0777; Male 0041; Female 0042; Mouse 0727; Mammal 0738; Animal model 0106; Biological models 0502; Controlled study 0197; Animal tissue, cells or cell components 0105; Priority journal 0007; Article 0060

DRUG DESCRIPTORS:
*cytokine--endogenous compound--ec; *autoantigen; *t lymphocyte antigen messenger rna--endogenous compound--ec; myelin basic protein; freund adjuvant

MEDICAL DESCRIPTORS:
*allergic encephalomyelitis--etiology--et; *allergic encephalomyelitis --prevention--pc; *autoimmunity--etiology--et; *autoimmunity--prevention --pc; *cellular immunity
immunization; disease resistance; t lymphocyte activation; t lymphocyte subpopulation; lymphocyte proliferation; immunological tolerance; adoptive transfer; disease severity; nonhuman; male; female; mouse; animal model; controlled study; animal tissue; animal cell; priority journal; article

EMCLAS DRUG CODES:

03700000000

CAS REGISTRY NO.: 9007-81-2

12/9/9 (Item 9 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11085011 BIOSIS Number: 97285011
Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM: Therapeutic intervention by immunostimulation?
Rabinovitch A
Room 430, Heritage Med. Res. Centre, Univ. Alberta, Edmonton, AB T6G 2S2, CAN
Diabetes 43 (5). 1994. 613-621.
Full Journal Title: Diabetes
ISSN: 0012-1797
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 001 Ref. 006656
The autoimmune response that leads to destruction of pancreatic islet beta-cells and insulin-dependent diabetes mellitus (IDDM) has a genetic basis; however, environmental factors can exert profound modulating effects on the genetic predisposition to this autoimmune response. Recent studies in animal models for human IDDM, the genetically diabetes-prone NOD mouse and BB rat, have revealed that microbial agents-including certain viruses and extracts of bacteria, fungi, and mycobacteria-often have a protective action against diabetes development. Many of these microbial preparations are immune adjuvants, which are agents that stimulate the immune system. The protective effects of these agents against diabetes appear to involve perturbations in the production of cytokines, which are polypeptides produced by and acting on cells of the immune system. Thus, recent studies in NOD mice suggest that the islet beta-cell-directed autoimmune response may be mediated by a T-helper 1 (Th1) subset of T-cells producing the cytokines interleukin-2 (IL-2) and interferon-gamma. These studies also suggest that the diabetes-protective effects of administering microbial agents, adjuvants, and a beta-cell autoantigen (GAD65 (glutamic acid decarboxylase)) may result from activation of a Th2 subset of T-cells that produce the cytokines IL-4 and IL-10 and consequently downregulate the Th1-cell-mediated autoimmune response. The clinical implication of these findings is that the autoinuntine response leading to islet beta-cell destruction and IDDM may be amenable to prevention or suppression by therapeutic interventions aimed at stimulating the host's own immunoregulatory mechanisms.
Descriptors/Keywords: LITERATURE REVIEW; HUMAN; RAT; INTERLEUKIN-2; INTERFERON-GAMMA; GLUTAMIC ACID DECARBOXYLASE; INTERLEUKIN-4; INTERLEUKIN-10 INSULIN-DEPENDENT DIABETES MELLITUS; AUTOIMMUNITY; PANCREAS; BETA-CELL; T HELPER TYPE 1
Concept Codes:
*02508 Cytology and Cytochemistry-Human
*03508 Genetics and Cytogenetics-Human
*10808 Enzymes-Physiological Studies
*12512 Pathology, General and Miscellaneous-Therapy (1971-)
*13004 Metabolism-Carbohydrates
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13020 Metabolism-Metabolic Disorders
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and

Reticuloendothelial System
*17002 Endocrine System-General
*17008 Endocrine System-Pancreas
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10068 Biochemical Studies-Carbohydrates
Biosystematic Codes:
86215 Hominidae
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Mammals; Primates; Humans; Nonhuman Vertebrates; Nonhuman Mammals; Rodents

12/9/8 (Item 8 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

11296596 BIOSIS Number: 97496596
Induction of interferon-gamma, interleukin-4, and transforming growth factor-beta in rats orally tolerized against experimental autoimmune myasthenia gravis
Wang Z-Y; Link H; Ljungdahl A; Hojeberg B; Link J; He B; Qiao J; Melms A; Olsson T
Dep. Biochem., CBS, Univ. Minnesota, 1479 Gortner Ave, St. Paul, MN 55108, USA
Cellular Immunology 157 (2). 1994. 353-368.
Full Journal Title: Cellular Immunology
ISSN: 0008-8749
Language: ENGLISH
Print Number: Biological Abstracts Vol. 098 Iss. 010 Ref. 132335
Oral administration of nicotinic acetylcholine receptor (AChR) to Lewis rats prior to myasthenogenic immunization with Torpedo AChR + complete Freund's adjuvant (CFA) results in the prevention of experimental autoimmune myasthenia gravis (EAMG) and the suppression of AChR-specific B cell responses and counteracts the development of AChR-reactive interferon-gamma (IFN-gamma) secreting T cells. To study the involvement of the T helper type 1 (Th1) cell-related lymphokine IFN-gamma, the Th2 cell-related interleukin-4 (IL-4), and transforming growth factor beta (TGF-beta) that suppresses the synthesis of IFN-gamma and IL-4, we used in situ hybridization with complementary DNA oligonucleotide probes to enumerate mononuclear cells (MNC) expressing mRNA for the cytokines IFN-gamma, IL-4, and TGF-beta. Upon in vivo recognition of AChR, popliteal, inguinal, and mesenteric lymph nodes, spleen and thymus of rats with EAMG contained higher levels of IFN-gamma, IL-4, and TGF-beta mRNA-expressing cells compared to CFA-injected control rats, implicating the involvement in EAMG of AChR-reactive Th1 and Th2 cells in parallel. TGF-beta was also upregulated in EAMG. Oral tolerance to EAMG was characterized by suppression of the levels of MNC expressing IFN-gamma and IL-4, but augmentation of cells expressing TGF-beta. The results suggest that IFN-gamma, IL-4, and TGF-beta are involved in the development of EAMG, and that TGF-beta is important in the induction of oral tolerance to EAMG.
Descriptors/Keywords: RESEARCH ARTICLE; TORPEDO; NICOTINIC ACETYLCHOLINE RECEPTOR; TH1 HELPER T CELL; TH2 HELPER T CELL; MONONUCLEAR CYTOKINE TRANSCRIPT EXPRESSION
Concept Codes:
*14004 Digestive System-Physiology and Biochemistry

*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*17002 Endocrine System-General
*17506 Muscle-Pathology
*20506 Nervous System-Pathology
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
02506 Cytology and Cytochemistry-Animal
03506 Genetics and Cytogenetics-Animal
10300 Replication, Transcription, Translation
19001 Dental and Oral Biology-General; Methods
22100 Routes of Immunization, Infection and Therapy

Biosystematic Codes:
85202 Chondrichthyes
86375 Muridae

Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Fish; Mammals; Nonhuman Mammals; Rodents

12/9/7 (Item 7 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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11807413 BIOSIS Number: 98407413

Prevention of Experimental Allergic Encephalomyelitis in Rats by Targeting Autoantigen to B Cells: Evidence That the Protective Mechanism Depends on Changes in the Cytokine Response and Migratory Properties of the Autoantigen-specific T Cells

Saoudi A; Simmonds S; Huitinga I; Mason D
Med. Res. Council Cell. Immunol. Unit, Sir William Dunn Sch. Pathol., Univ. Oxford, Oxford OX1 3RE, UK

Journal of Experimental Medicine 182 (2). 1995. 335-344.
Full Journal Title: Journal of Experimental Medicine
ISSN: 0022-1007
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 006 Ref. 085005

Previous experiments from this laboratory have shown that Lewis rats were protected from experimental allergic encephalomyelitis (EAE) induced by the injection of myelin basic protein (MBP) in Freund's complete adjuvant if they were treated with the encephalitogenic peptide of MBP covalently linked to mouse anti-rat immunoglobulin (Ig) D. It was suggested that this protection developed because the antibody-peptide conjugate targeted the peptide to B cells and that this mode of presentation induced a Th2-like T cell response that controlled the concomitant encephalitogenic Th1 reaction to the autoantigen. The current experiments were carried out to test this hypothesis and to examine the alternative explanation for the protective effect of the conjugate pretreatment, namely that it induced a state of nonresponsiveness in the autoantigenspecific T cells. It was shown that EAE induction was suppressed in Lewis rats when the antibody-peptide conjugate was injected intravenously 14 and 7 d before immunization with MBP in adjuvant, but that anti-MBP antibody titers were at least as high in these animals as in controls that were not pretreated with the conjugate before immunization. Lymph node cells from these pretreated animals, while proliferating in vitro to MBP as vigorously as those from controls, produced less interferon gamma and were very inferior in their ability to transfer disease after this in vitro activation. In contrast, these same

lymph node cells from protected rats generated markedly increased levels of messenger RNA for interleukin (IL)-4 and IL-13. When these in vitro experiments were repeated using the encephalitogenic peptide rather than MBP as the stimulus, the proliferative response of lymph node cells from pretreated donors was less than that from controls but was still readily detectable in the majority of experiments. Furthermore, the cytokine expression induced by the peptide was similar to that elicited by whole MBP. While these results support the original hypothesis that the anti-IgD-peptide conjugate pretreatment protected rats from EAE by inducing a Th2-type cytokine response, a totally unexpected finding was that this pretreatment greatly reduced the level of leukocyte infiltration into the central nervous system. This result provides a direct explanation for the protective effect of the pretreatment, but it raises questions regarding migratory and homing patterns of leukocytes activated by different immunological stimuli.

Descriptors/Keywords: RESEARCH ARTICLE; MESSENGER RNA; INTERLEUKIN-4; INTERLEUKIN-13; MYELIN BASIC PROTEIN; AUTOIMMUNE DISEASE; LYMPH NODE; LEUKOCYTE HOMING PATTERN

Concept Codes:

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  *02506   Cytology and Cytochemistry-Animal
  *12508   Pathology, General and Miscellaneous-Inflammation and
           Inflammatory Disease
  *15004   Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
  *15008   Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and
           Reticuloendothelial System
  *17002   Endocrine System-General
  *20506   Nervous System-Pathology
  *34508   Immunology and Immunochemistry-Immunopathology, Tissue
           Immunology
  *35500   Allergy
   10062   Biochemical Studies-Nucleic Acids, Purines and Pyrimidines
   10064   Biochemical Studies-Proteins, Peptides and Amino Acids
   10068   Biochemical Studies-Carbohydrates
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Biosystematic Codes:

```
   86375   Muridae
```

Super Taxa:

Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

?ds

Set	Items	Description
S1	0	TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
S2	1174	E1-E31
S3	129	E1-E14
S4	1303	S2 OR S3
S5	15	S4 AND TH2
S6	8	RD (unique items)
S7	23	TH2 AND AUTOIMMUN
S8	1403	TH2 AND AUTOIMMUN?
S9	120	S8 AND ADJUVANT?
S10	120	S9
S11	78	RD (unique items)
S12	78	S11 NOT S6

?s s8 and ifa

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            1403   S8
            8092   IFA
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    S13      16  S8 AND IFA
?rd

>>>Duplicate detection is not supported for File 42.
>>>Duplicate detection is not supported for File 43.
>>>Duplicate detection is not supported for File 94.
>>>Duplicate detection is not supported for File 129.
>>>Duplicate detection is not supported for File 130.
>>>Duplicate detection is not supported for File 140.
>>>Duplicate detection is not supported for File 187.
>>>Duplicate detection is not supported for File 286.
>>>Duplicate detection is not supported for File 428.
>>>Duplicate detection is not supported for File 429.
>>>Duplicate detection is not supported for File 446.
>>>Duplicate detection is not supported for File 449.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 455.
>>>Duplicate detection is not supported for File 456.
>>>Duplicate detection is not supported for File 350.
>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
    S14       9  RD (unique items)
?t s14/3/1-9
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14/3/1   (Item 1 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
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13088216   BIOSIS Number: 99088216
Antigen based therapies to prevent diabetes in NOD mice
Ramiya V K; Shang X-Z; Pharis P G; Wasserfall C H; Stabler T V; Muir A B; Schatz D A; Maclaren N K
Dep. Pathol. Lab. Med., PO Box 100275, Univ. Fla., Gainesville, FL 32610-0275, USA
Journal of Autoimmunity 9 (3). 1996. 349-356.
Full Journal Title: Journal of Autoimmunity
ISSN: 0896-8411
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 004 Ref. 053665

14/3/2   (Item 2 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

13039712   BIOSIS Number: 99039712
Heat shock proteins and experimental autoimmune encephalomyelitis (EAE): I. Immunization with a peptide of the myelin protein 2',3' cyclic nucleotide 3' phosphodiesterase that is cross-reactive with a heat shock protein alters the course of EAE
Birnbaum G; Kotilinek L; Schlievert P; Clark H B; Trotter J; Horvath E; Gao E; Cox M; Braun P E
Dep. Neurol., Univ. Minnesota, Box 295, UMHC, Minneapolis, MN 55455, USA
Journal of Neuroscience Research 44 (4). 1996. 381-396.
Full Journal Title: Journal of Neuroscience Research

ISSN: 0360-4012
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 002 Ref. 021885

14/3/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

12064539 BIOSIS Number: 98664539
Neonatal or adult injection of MBP in IFA induces a vigorous TH2-type T cell response
Forsthuber T; Cheng H; Karulin A; Lehman P
Case Western Reserve Univ., Sch. Med., Dep. Pathol., Cleveland, OH 44106, USA
Journal of Neuroimmunology 0 (SUPPL. 1). 1995. 66.
Full Journal Title: 11th European Congress on Multiple Sclerosis. Journal of Neuroimmunology
ISSN: 0165-5728
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 003 Ref. 040364

14/3/4 (Item 1 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01646642 SUPPLIER NUMBER: 18732757 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The hsp60 peptide p277 arrests the autoimmune diabetes induced by the toxin streptozotocin.
Elias, Dana; Cohen, Irun R.
Diabetes, v45, n9, p1168(5)
Sep, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3933 LINE COUNT: 00307

14/3/5 (Item 2 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01497540 SUPPLIER NUMBER: 15981856 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Immunization with the larger isoform of mouse glutamic acid decarboxylase (GAD67) prevents autoimmune diabetes in NOD mice. (non-obese diabetic mice)
Elliott, John F.; Qin, Hui-Yu; Bhatti, Sunita; Smith, Dean K.; Singh, Raj Kumari; Dillon, Tom; Lauzon, Jana; Singh, Bhagirath
Diabetes, v43, n12, p1494(6)
Dec, 1994
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 5036 LINE COUNT: 00414

14/3/6 (Item 3 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)

(c) 1997 Info Access Co. All rts. reserv.

01424304 SUPPLIER NUMBER: 14105587 (USE FORMAT 7 OR 9 FOR FULL TEXT)
The 12th International Immunology and Diabetes Workshop: Orlando, Florida.
Maclaren, Noel; Lafferty, Kevin
Diabetes, v42, n8, p1099(6)
August, 1993
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 4432 LINE COUNT: 00440

14/3/7 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15123610 Genuine Article#: VL103 No. References: 23
Title: GENETIC SUSCEPTIBILITY TO EXPERIMENTAL AUTOIMMUNE UVEORETINITIS IN THE RAT IS ASSOCIATED WITH AN ELEVATED TH1 - RESPONSE
Author(s): CASPI RR; SILVER PB; CHAN CC; SUN B; AGARWAL RK; WELLS J; ODDO S ; FUJINO Y; NAJAFIAN F; WILDER RL
Corporate Source: NEI,IMMUNOL LAB,NIH,BLDG 10,ROOM 10N222,10 CTR DR,MSC 1858/BETHESDA//MD/20892; NIAMSD,NATL INST HLTH/BETHESDA//MD/20892
Journal: JOURNAL OF IMMUNOLOGY, 1996, V157, N6 (SEP 15), P2668-2675
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

14/3/8 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
(c) 1997 Inst for Sci Info. All rts. reserv.

15033202 Genuine Article#: VE109 No. References: 28
Title: IL-12 PROMOTES CELLULAR BUT NOT HUMORAL TYPE-II COLLAGEN-SPECIFIC T(H)1-TYPE RESPONSES IN C57BL/6 AND B10.Q MICE AND FAILS TO INDUCE ARTHRITIS
Author(s): SZELIGA J; HESS H; RUDE E; SCHMITT E; GERMANN T
Corporate Source: INST IMMUNOL,OBERE ZAHLBACHER STR 67/D-55101 MAINZ//GERMANY/; INST IMMUNOL/D-55101 MAINZ//GERMANY/
Journal: INTERNATIONAL IMMUNOLOGY, 1996, V8, N8 (AUG), P1221-1227
ISSN: 0953-8178
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

14/3/9 (Item 1 from file: 636)
DIALOG(R)File 636:IAC Newsletter DB(TM)
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03259419
Autoimmune Encephalomyelitis: Birnbaum, G.; Kotilinek, L.; Schlievert, P.; Clark, H.B.; Trotter, J.; Horvath, E.; Gao, E.; Cox, M.; Braun, P.E. "Heat Shock Proteins and Experimental Autoimmune Encephalomyelitis (EAE) .1. Immunization with a Peptide of the Myelin Protein 2',3' Cyclic Nucleotide 3' Phosphodiesterase That Is Cross-Reactive with a Heat Shock Protein Alters the Course of EAE."
Vaccine Weekly July 8, 1996
ISSN: 1074-2921 WORD COUNT: 327
PUBLISHER: Charles W Henderson

?t s14/9/1-9

14/9/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13088216 BIOSIS Number: 99088216

Antigen based therapies to prevent diabetes in NOD mice

Ramiya V K; Shang X-Z; Pharis P G; Wasserfall C H; Stabler T V; Muir A B; Schatz D A; Maclaren N K

Dep. Pathol. Lab. Med., PO Box 100275, Univ. Fla., Gainesville, FL 32610-0275, USA

Journal of Autoimmunity 9 (3). 1996. 349-356.
Full Journal Title: Journal of Autoimmunity
ISSN: 0896-8411
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 004 Ref. 053665

Interventional approaches that have been successful in delaying insulin-dependent diabetes mellitus (IDDM) using antigen-based immunotherapies include parenteral immunization. It has potential for clinical application provided that effective adjuvants suitable for human use can be found. We have previously shown that immunization with insulin and insulin B chain but not A chain in incomplete Freund's adjuvant (IFA) prevented diabetes by reducing IFN-gamma mRNA in the insulitis lesions. In this paper we show that the insulin B chain peptide (p9-23) contain the most protective epitope. Immunization with selected GAD peptides was ineffective. Immunization with B chain but not A chain using alum as adjuvant delayed diabetes onset (P=0.012), whereas administration of alum alone was not protective. When Diphtheria-Tetanus toxoid-Acellular Pertussis (DTP) vaccine was used as the adjuvant vehicle, DTP itself induced significant protection (P lt 0.003) which was associated with a Th2-like cytokine producing insulitis profile, IL-4 driven IgG1 antibody responses to insulin, GAD in the periphery and an augmentation of the autoimmune response to GAD. The anti-diabetic effect of DTP was enhanced when given with insulin B chain. These results encourage consideration of an approach using alum/DTP and insulin B chain immunization in clinical trials.

Descriptors/Keywords: RESEARCH ARTICLE; NONOBESE DIABETIC MOUSE; ADJUVANT; CYTOKINE; DIPHTHERIA-TETANUS TOXOID-ACELLULAR PERTUSSIS VACCINE; AUTOIMMUNITY; ALUM; ANTIBODIES

Concept Codes:
*02506 Cytology and Cytochemistry-Animal
*03506 Genetics and Cytogenetics-Animal
*10054 Biochemical Methods-Proteins, Peptides and Amino Acids
*10058 Biochemical Methods-Carbohydrates
*12512 Pathology, General and Miscellaneous-Therapy (1971-)
*13004 Metabolism-Carbohydrates
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13020 Metabolism-Metabolic Disorders
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*17008 Endocrine System-Pancreas
*22016 Pharmacology-Endocrine System
*22018 Pharmacology-Immunological Processes and Allergy
*25508 Developmental Biology-Embryology-Morphogenesis, General
*34502 Immunology and Immunochemistry-General; Methods

*34504 Immunology and Immunochemistry-Bacterial, Viral and Fungal
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
*36002 Medical and Clinical Microbiology-Bacteriology
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10068 Biochemical Studies-Carbohydrates
22005 Pharmacology-Clinical Pharmacology (1972-)

Biosystematic Codes:
06502 Alcaligenaceae (1992-)
07810 Endospore-forming Gram-Positives (1992-)
08890 Irregular Nonsporing Gram-Positive Rods (1992-)
86375 Muridae

Super Taxa:
Microorganisms; Bacteria; Eubacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

14/9/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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13039712 BIOSIS Number: 99039712

Heat shock proteins and experimental autoimmune encephalomyelitis (EAE): I. Immunization with a peptide of the myelin protein 2',3' cyclic nucleotide 3' phosphodiesterase that is cross-reactive with a heat shock protein alters the course of EAE

Birnbaum G; Kotilinek L; Schlievert P; Clark H B; Trotter J; Horvath E; Gao E; Cox M; Braun P E
Dep. Neurol., Univ. Minnesota, Box 295, UMHC, Minneapolis, MN 55455, USA
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Print Number: Biological Abstracts Vol. 102 Iss. 002 Ref. 021885

We describe sequence similarity and immunologic cross-reactivity between a peptide of the mycobacterial hsp, HSP65, and the myelin protein 2',3' cyclic nucleotide 3' phosphodiesterase (CNP). We demonstrate that immunization with the homologous crossreactive CNP peptide (hsp-CNP peptide) has significant biological consequences. Rats immunized with hsp-CNP peptide in either complete Freund's adjuvant (CFA) or incomplete Freund's adjuvant (IFA) produce large amounts of peptide-specific antibody. Isotypes of antibodies in animals immunized with peptide in CFA are IgG1 and IgG2a. Isotypes of antibodies in rats immunized with peptide in IFA are predominantly IgG1, with low titers of IgG2a. T cell proliferative responses to HSP65 are present in rats immunized with peptide in CFA. T cell responses to HSP65 initially are absent in rats immunized with peptide in IFA but develop over time. T cell proliferative responses to hsp-CNP peptide were not detected. None of the groups of rats developed clinical or histologic evidence of experimental autoimmune encephalomyelitis (EAE). To induce EAE, rats preimmunized with hsp-CNP peptide were challenged with guinea pig spinal cord (GPSC) emulsified in CFA. Rats preimmunized with peptide in CFA developed severe EAE. Rats preimmunized with hsp-CNP peptide in IFA were protected from EAE, with both a lower incidence and severity of disease. Injecting the murine monoclonal antibody recognizing the shared HSP65 and CNP epitope did not protect against EAE. Our data suggest that a Th2 pattern of immune response to a CNP peptide that itself is non-encephalitogenic protects against EAE. Immune responses to either hsp or myelin proteins cross-reactive with hsp may play an important role in

the development of EAE.
Descriptors/Keywords: RESEARCH ARTICLE; RAT; IMMUNOGLOBULIN G; DEMYELINATION; PATHOGENESIS
Concept Codes:
*12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
*13004 Metabolism-Carbohydrates
*13006 Metabolism-Lipids
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13020 Metabolism-Metabolic Disorders
*20506 Nervous System-Pathology
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10618 External Effects-Temperature as a Primary Variable-Hot (1971-)
10808 Enzymes-Physiological Studies
12008 Physiology, General and Miscellaneous-Stress (1970-)
Biosystematic Codes:
86375 Muridae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

14/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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12064539 BIOSIS Number: 98664539
Neonatal or adult injection of MBP in IFA induces a vigorous TH2-type T cell response
Forsthuber T; Cheng H; Karulin A; Lehman P
Case Western Reserve Univ., Sch. Med., Dep. Pathol., Cleveland, OH 44106, USA
Journal of Neuroimmunology 0 (SUPPL. 1). 1995. 66.
Full Journal Title: 11th European Congress on Multiple Sclerosis. Journal of Neuroimmunology
ISSN: 0165-5728
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 003 Ref. 040364
Descriptors/Keywords: MEETING ABSTRACT; MEETING POSTER; MYELIN BASIC PROTEIN; INTERLEUKIN-4; INTERLEUKIN-5; INTERFERON-GAMMA; EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS; AUTOIMMUNE DISEASE
Concept Codes:
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*17002 Endocrine System-General
*20506 Nervous System-Pathology
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
02506 Cytology and Cytochemistry-Animal
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
25000 Pediatrics
Biosystematic Codes:

33000 Animalia-Unspecified
Super Taxa:
Animals

14/9/4 (Item 1 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01646642 SUPPLIER NUMBER: 18732757 (THIS IS THE FULL TEXT)
The hsp60 peptide p277 arrests the autoimmune diabetes induced by the toxin streptozotocin.
Elias, Dana; Cohen, Irun R.
Diabetes, v45, n9, p1168(5)
Sep, 1996
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3933 LINE COUNT: 00307

TEXT:

The development of autoimmune diabetes in the NOD strain of mice (H-(2.sup.g7)) is marked by the presence of T-cells reactive to the p277 peptide of the 60-kDa heat shock protein (hsp60). We have found that the p277 peptide can be used as a therapeutic vaccine to arrest NOD diabetes. Recently, we found that T-cell autoimmunity to p277 also develops spontaneously in C57BL/KsJ mice (H-(2.sup.d)) during the induction of autoimmune diabetes by a very low dose of the (beta)-cell toxin streptozotocin (STZ). We now report the inhibition of STZ toxin-induced autoimmune diabetes by p277 peptide therapy. Administration of two doses each of 100 (mu)g of peptide p277 in mineral oil given 1 week after toxin induction and 85 days later was most effective. The effect of p277 on STZ toxin-induced diabetes was marked by a shift in p277 autoimmunity from a T-cell proliferative response to the production of anti-p277 antibodies. The anti-p277 antibodies were predominantly of the IgG1 and IgG2b isotypes, known to be regulated by Th2 type cytokines; IgG2a antibody, known to be dependent on interferon (IFN)-(gamma), was induced to a much lesser degree. Peptide p277 therapy was specific: treatment of the mice with an immunogenic peptide from the sequence of another antigen, GADp34, failed to prevent the development of diabetes. The GADp34 peptide induced lower titers of specific antibodies, and the antibodies were predominantly of the IgG2a class. Thus, p277 peptide therapy, marked by the induction of Th2-type antibodies, can be effective in toxin-induced autoimmune diabetes.
Diabetes 45:1168-1172, 1996

We recently reported that it was possible to induce remission of advanced insulitis, even after the clinical onset of overt diabetes, by treating NOD mice with a peptide from the sequence of the human 60-kDa heat shock protein (hsp60) (1,2). This peptide, designated p277, is composed of the 24 amino acids spanning positions 437-460 of hsp60. Treatment of NOD diabetes using peptide p277 was found to downregulate spontaneous T-cell reactivity to the p277 portion of hsp60 (3), a T-cell reactivity that can cause diabetes (4). Thus, a peptide containing an epitope targeted by diabetogenic T-cells can be used as a therapeutic agent to turn off a spontaneous diabetogenic process.

We have found that a form of autoimmune diabetes can be induced in the C57BL/XsJ strain of mice by the administration of a very low dose of the (beta)-cell toxin streptozotocin (STZ) (5). Whereas the standard low dose of STZ of 40 mg/kg administered daily for 5 days usually induces clinical diabetes within 3 weeks, the administration of 30 mg/kg for 5 days

induces clinical diabetes only after a lag period of 3 months. This model of induced diabetes is marked by spontaneous autoimmunity to hsp60 and to its p277 peptide and to insulin (5). Thus, the lower-than-standard low dose of STZ appears to trigger an autoimmune process immunologically similar to that observed in the spontaneous diabetes developing in NOD mice (3,6). Because treatment with peptide p277 was effective in reversing the diabetogenic process in NOD mice, we investigated whether p277 treatment might also modify the autoimmune response and thereby abort the development of the diabetes induced by the very low dose of STZ. The present paper demonstrates this to be the case.

RESEARCH DESIGN AND METHODS

Induction of diabetes. Male mice of the C57BL/KsJ strain, 4 weeks old, were purchased from Jackson Laboratories (Bar Harbor, ME) and used after 2 weeks of acclimatization to our animal house. The mice were treated with five daily doses of 30 mg kg of STZ i.p., purchased from Boehnnger Mannheim (Mannheim, Germany), to induce diabetes as described (5). Blood glucose was measured at regular intervals using a Beckman Glucose Analyzer (Palo Alto, CA) to determine the development of diabetes. In these studies, significant hyperglycemia was judged to be a blood glucose concentration >15 mmol/1.

Peptides and treatment. Peptide p277 was synthesized by standard Fmoc chemistry using an automated ABIMED synthesizer (I,angenfeld, Germany) as described (1,2). The sequence of p277 is VLGGGCALLRCIPALDSLTPANED. The p277 peptide in its native sequence tends to be chemically unstable, probably because of the two cystein (C) residues. To obtain a form of p277 that is more chemically stable, we have substituted the two cysteins with two valine (V) residues to produce a peptide that is immunologically the equivalent of the native sequence (D.E., I.R.C., unpublished observations). The studies reported here have been done using both forms of p277 with equivalent results. Figures 1 and 2 present results with the native sequence, and Figures 3-6 show results using the V-substituted peptide. The p277 peptides were purified by reverse-phase high-performance liquid chromatography, and the composition was confirmed by amino acid analysis. Three peptides of the 65-kDa isotype of the antigen GAD65 were prepared and purified as above and included peptide 17 (GADp17) (residues 247-266) NMYAMMIARIKMFPEVKEKG; peptide 34 (GADp34) (residues 509-528) IPPSLRTLEDNEERMSRLSK; and peptide 35 (GADp:35) (residues 524-543) SRLSKVAPVIKARMMEYGTT (7). Mice received a subcutaneous inoculation of 100 (mu)g of p277 or of GADp34 in phosphate-buffered saline (PBS) emulsified in an equal volume of incomplete Freund's adjuvant (IFA; mineral oil with emulsifying agent) purchased from Difco (Detroit, MI). A total volume of 0.1 ml was injected subcutaneously under the skin of the back. Control treatment consisted of an emulsion of PBS in IFA without p277 or GADp34. Three different treatment schedules were tested: one treatment 14 days before STZ induction (day -14), one treatment 7 days after onset of STZ induction (day +7), and two treatments given 7 and 85 days after onset of STZ induction (days +7, +85).

T-cell proliferation. To investigate the specific immunogenicity of peptides p277 and GADp34 in C57BL/KsJ strain mice, groups of five mice were immunized in the hind foot pads with either peptide (100(mu)g) emulsified in 0.1 ml IFA. Ten days later, the draining lymph node lymphocytes were tested for their proliferative responses to either peptide, as described below. To assay the effects of STZ induction and peptide treatment on the proliferative response, spleens were removed on day 58 from mice inoculated with five daily doses of 30 mg/kg of STZ and treated with p277 in IFA on day 7 after induction by STZ. Control mice were treated with an emulsion of PBS and IFA. Five mice of each group were killed and their spleens tested separately in a T-cell proliferation assay, as described (3,4). Briefly, splenocytes were seeded in quadruplicate wells in microtiter plates, 0.2 x

106 cells in 0.2 ml of Dulbecco's modified Eagle's medium supplemented with 1% autologous serum for 72 h. Antigens were added at a concentration of 10 (mu)g/ml. The antigens tested were peptide p277 and the three peptides of GAD65. The wells were pulsed with ((sup.3)H)-labeled thymidine for the last 18 h of culture, the cells were harvested, and the incorporated radioactivity was counted in a ,(Beta)-counter. The stimulation index (SI) was defined as the ratio of the antigen-driven thymidine incorporation to the background incorporation in the absence of antigen. Background counts per minute were in the range of 1,000-2,000. Standard deviations were <10% of the mean.

Antibodies. Antibodies to p277 or GADp34 peptides were assayed in the sera of treated or control mice bled 100 days after the administration of STZ. A standard enzyme-linked immunosorbent assay (ELISA) was used, as described (5,6). Briefly, 10(mu)g of the peptides were applied to assay plates (Maxisorp, Nunc Roskilde, Denmark) suitable for the binding of peptides, and the plates were incubated with the test sera. The binding of antibodies to the adherent peptides was detected using alkaline phosphatase conjugated anti-mouse IgG + IgM or isotypespecific anti-mouse IgG1, IgG2a, or IgG2b (Jackson ImmunoResearch, West Grove, PA). A significant amount of antibody was defined as an optical density (OD) 405-nm reading of 0.25, which is 3 SD over the mean ELISA reading obtained in the sera of 10 normal BALB/c mice.

RESULTS

Treatment with p277. Treatment of NOD mice with peptide p277 was found to be effective both when administered early during the course of disease before appreciable insulitis (3) and when administered late after the initiation of the diabetogenic process (1,2). We therefore administered p277 to C57BL/KsJ mice both before and after we induced a diabetogenic process by exposing the mice to the very low dose of STZ (30 mg/kg x 5). Figure 1A shows the course of hyperglycemia developing in the control groups of mice given PBS in the IFA vehicle either 14 days before STZ induction (day - 14) or at days 7 and 85 (days + 7, +85) after induction. It can be seen that by day 240, all of the mice were diabetic with blood glucose concentrations between 32.5 and 42.5 mmol/1. In contrast, the mice treated with p277 14 days (day - 14) before STZ induction showed a significantly decreased degree of hyperglycemia; range 25-32 mmol/1, P = 0.01 (Fig. 1B). In addition, we treated mice with p277 after the induction of the diabetogenic process. Figure 1C shows that p277 administered 7 days after the beginning of the 5-day course of STZ (day +7) also lowered the final level of hyperglycemia (P = 0.003 compared with Fig. 1A). Since moderate hyperglycemia was observed on day 80 in all mice treated, we administered a second dose of p277 on day 85. Figure 1D shows that this second dose did in fact turn off the diabetogenic process: the mice treated with p277 on days 7 and 85 manifested a transient hyperglycemia around day 80 that remitted; all the mice were normoglycemic 240 days after STZ induction.

T-cell proliferation. The success of peptide p277 in treating the spontaneous diabetes of NOD mice was associated with a decrease in T-cell proliferative reactivity to hsp60 and to the p277 peptide itself (2,3). Figure 2 shows that p277 treatment of the test C57BL/KsJ mice was similarly associated with downregulation of their spontaneous T-cell proliferative response to p277. T-cell responses to three peptides of the GAD65 antigen have been reported to occur spontaneously in NOD mice (7), so we tested the T-cell responses of the mice to the GAD65 peptides. Figure 2 shows that the STZ administration induced only negligible T-cell responses (SI = 2) to the GADp17 and GADp34 peptides.

To test whether peptide GADp34 was indeed a specific T-cell epitope in C57BL/KsJ mice, we immunized naive mice against either p277 or GADp34

and tested the proliferative responses. Figure 3 shows that the C57BL/KsJ mice were able to manifest specific responses to each peptide, although the response to GADp34 was somewhat lower than the response to p277. Thus, GADp34 is immunogenic for T-cells in these mice. Because GAD65 was found to be functional in treating NOD mice (7), we tested whether therapy with the GADp34 peptide, like p277 therapy, might be effective in the STZ model.

Treatment with p277 compared with GADp34. Groups of C57BL/KsJ mice received STZ (30 mg/kg x 5) to induce autoimmune diabetes, and the mice were treated with either p277 or with GADp34 peptide in IFA on days 7 and 85. The levels of blood glucose were tested on day 100. Figure 4 shows that the mice treated with GADp34, like the control mice treated with PBS, were markedly hyperglycemic; there was no significant difference between these two groups. In contrast, 6 of the 10 mice treated with p277 manifested blood glucose concentrations <15 mmol/1, two additional mice were just over the 15 mmol/1 borderline, and only two mice were frankly hyperglycemic, one of them markedly so. As a whole, the mean blood glucose concentration of the p277 treated group was significantly lower than that of the other two groups of mice. Thus, therapy with peptide p277 was specific.

Peptide p277 induces antibodies. It has been suggested that a shift from an effector T-cell response (Th1-type) to an antibody response (Th2-type) might be therapeutic in autoimmune diabetes (8). Indeed, Fig. 5 shows that high levels of anti-p277 antibodies were induced by p277 treatment in the STZ model. The anti-p277 antibodies were specific; the sera from the p277-treated mice showed no significant binding to peptide GADp34. Note that the two p277-treated mice that made low levels of anti-p277 antibodies were the two mice that developed gross hyperglycemia (20 mmol/1 or greater) in the p277 group (Fig. 4). Treatment with peptide GADp34 also induced antibodies to GADp34 and to p277 in most of the treated mice (OD 405 nm >0.25), but the amounts of antibodies appeared to be lower than those induced by treatment with p277.

Antibody isotypes. Th2 type antibodies can be identified by their Ig isotypes; interleukin (IL)-4 is thought to induce antibodies of the IgG1 isotype (9) and transforming growth factor (TGF)-(Beta) is thought to induce IgG2b antibodies (10). In contrast, the Thl cytokine IFN-(Gamma) induces antibodies of the IgG2a isotype (9). Figure 6 shows the isotypes of the anti-p277 antibodies in the p277-treated mice. It can be seen that the anti-p277 antibodies in the p277-treated mice were predominantly of the IgG1 and IgG2b isotypes. In contrast, the anti-GADp34 antibodies in the GADp34-treated mice were predominantly of the IgG2a isotype. Thus, p277 peptide therapy appears to induce antibodies that reflect a predominant Th2-type response. Peptide GADp34, which was not effective, induced lower titers of antibodies, mainly of the Th-1 type.

DISCUSSION

The effectiveness of p277 peptide therapy in STZ toxin induced diabetes raises two general questions: what is the role of p277 immunity in this model of diabetes, and how does administration of the p277 peptide arrest the disease? We can consider these questions in the light of studies of the NOD model of autoimmune diabetes where more information about the role of p277 is available. The sequence of the p277 peptide used in these studies was derived from the human hsp60 molecule, and the human p277 peptide differs from the mouse p277 analog by one amino acid substitution, K for T at position 455 (11). Nevertheless, the human and mouse variants of p277 are immunologically cross-reactive, and the mouse p277 peptide is as effective as the human analog in treating NOD diabetes (11). Thus, the human p277 sequence probably functions in mice as if it were a part of the mouse hsp60 self-antigen.

It is reasonable to suppose that the stress caused by exposure to STZ can alter the amount and/or the nature of the presentation of hsp60 in

(Beta)-cells. Indeed, we find that a ,(Beta)-cell tumor line (NIT-1) responds to STZ in vitro by upregulating the surface expression of hsp60; an increase in surface hsp60 in response to STZ is not shown by cells originating from other tissues (A. Meilin, D.E., I.R.C., unpublished observations). Thus, STZ might induce a special expression of hsp60 in (Beta)-cells. However, this by itself cannot explain the association of STZ-induced diabetes with hsp60 autoimmunity, and more research is needed to uncover the molecular mechanisms involved in p277 as a target of autoimmune T-cells in diabetes (5).

The role of p277 in diabetes is complicated by the fact that forms of hsp60 autoimmunity also may be involved in the pathogenesis of other immunological diseases, including arthritis (12) and encephalomyelitis (13). But whatever the role of hsp60 autoimmunity in other diseases may be, autoimmunity to hsp60 seems to be involved in (Beta)-cell damage. We have created transgenic NOD mice that hyperexpress mouse hsp60 in the thymus and elsewhere directed by a mouse major histocompatibility complex class II promoter, IE (Alpha) (14). These mice demonstrate a form of tolerance to hsp60 manifested by the absence of the spontaneous T-cell proliferative response to p277 present in wild type NOD mice. Interestingly, the hsp60 transgenic mice develop pert-islet insulitis, but the inflammation does not proceed to the stage of intra-islet insulitis and clinical diabetes (14). Thus, T-cell reactivity to p277 may be critical for (Beta)-cell destruction.

The present finding that p277 therapy led to deviation of p277 autoimmunity from proliferating T-cells to anti-p277 antibodies supports the notion that arrest of 3-cell damage might be brought about by inducing a switch from a Thl effector T-cell response to autoimmunity of the Th2 type (8). The observation that p277 therapy induced a predominance of IgG1 and IgG2b antibodies to p277 can be seen as functional evidence for the role of IL-4 and TGF-(Beta) in the response to p277 therapy. We are currently developing methods to document the quantities of these anti-inflammatory cytokines in the islets, and direct proof for the induction of a switch to Th2 cytokines awaits this methodology. However, compatible with the induction of anti-inflammatory suppresser cytokines is our finding that activated T-cells from p277-treated NOD mice could suppress diabetes in an adoptive transfer experiment (2). Thus, protection from the development of diabetes need not require the deactivation or deletion of anti-p277 autoimmunity but rather the activation of a shift in the type of autoimmunity (15-17).

It is interesting that immunization with peptide GADp34 did not cure the diabetic process. Peptide GADp34 is clearly immunogenic in C57BL/KsJ mice; a single injection of 100 (mu)g in IFA sufficed to induce a significant T-cell proliferative response (mean SI = 7; Fig. 3), and treatment with GADp34 in the STZ model did induce significant titers (OD 405 nm > 0.25) of IgG2a antibodies in most mice (Fig. 6). Because GADp34 represents an immunogenic self-peptide, it may be viewed as a control for p277 peptide treatment. Despite the immunogenicity of GADp34 for C57BL/KsJ mice, however, the spontaneous T-cell response to GADp34 associated with STZ induction of diabetes was very low (Fig. 2). This suggests that the GADp34 peptide may not be a target in the model. In contrast, induction of diabetes by the administration of STZ was associated with spontaneous activation of a strong anti-p277 T-cell response (Fig. 2) (5); hence, immunity to p277 is intrinsic to the model. Thus, the mice may have already been primed to respond to p277 by the disease process itself, laying the foundation for the positive response to p277 peptide therapy (15). The prominent immunogenicity of p277 notwithstanding, it is intriguing that the failure of GADp34 compared with the success of p277 might be correlated with the ability of GADp34 to induce specific antibody predominantly of the

IgG2a isotype associated with aTh1-type response.

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(Figures 1 to 6 ILLUSTRATION OMITTED)

REFERENCES

(1.) Elias D, Cohen IR: Peptide therapy for diabetes in NOD mice. Lancet 343:704-706, 1994 (2.) Elias D, Cohen IR: Treatment of autoimmune diabetes and insulitis in NOD mice with heat protein 60 peptide p277. Diabetes 44:1132-1138, 1995 (3.) Elias D, Reshef T, Birk OS, van der Zee R, Walker MD, Cohen IR: Vaccination against autoimmune mouse diabetes with a T-cell epitope of the human 65 kDa heat shock protein. Proc NaU Acad Sci USA 88:30883091, 1991 (4.) Elias D, Marcus H, Reshef T, Ablamunits V, Cohen IR: Induction of diabetes in standard mice by immunization with the p277 peptide of a 60-kDa heat shock protein. Eur J Immunol 25:2851-2857, 1995 (5.) Elias D, Prigozm H, Polak N, Rapoport M, Lobse AW, Cohen IR: Autoimmume diabetes induced by the (Beta)-cell toxin streptozotocm: immunity to the 60-kDa heat shock protein and to insulin. Diabetes 43:992-998, 1994 (6.) Elias D, Markovits D, Reshef T, van der Zee R, Cohen IR: Induction and therapy of autoimmune diabetes in the non-obese diabetic (NOD/IT) mouse by a 65-kDa heat shock protein. Proc NaU Acad Sci USA 87:1576-1580, 1990 (7.) Kaufman DL, Clare-Salzler M, Tian J, Forsthuber T, Ting GSP, Robinson P, Atkmson MA, Sercarz EE, Tobin AJ, Lehmann PV: Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. Nature 366:69-72, 1993 (8.) Liblau RS, Singer SM, McDevut HO: Thl and Th2 CD4+ T-cells in the pathogenesis of organ-specific autoimmume diseases. Immunol Today 16:34-38, 1995 (9.) Snapper CM, Mond JJ: Towards a comprehensive view of immumoglobulin class switching. Immunol Today 14:15-17, 1993 (10.) Snapper CM, Waegell W, Beernink H, Dasch JR: Transforming growth factor-beta 1 is required for secretion of IgG of all subclasses by LPS-activated murine B in cells in vitro. J Immunol 151:4625-4636, 1993 (11.) Birk OS, Elias D, Weiss AS, Rosen A, van der Zee R, Walker MD, Cohen IR: NOD mouse diabetes: the ubiquitous mouse hsp60 is a beta-cell target antigen of autoimmune T cells. J Autoimmun 9:159-166, 1996 (12.) Cohen IR: Autoimmunity to chaperonins m the pathogenesis of arthritis and diabetes. Annu Rev Immunol 9:567-589, 1991 (13.) Mor F, Cohen IR: T cells in the lesion of experimental autoimmume encephalomyelitis: enrichment for reactivities to myelin basic protein and to heat shock proteins. J Clin Invest 90:2447-2455, 1992 (14.) Birk OS, Douek DC, Elias D, Takacs K, Dewchand H, Gur SL, Walker MD, van der Zee R, Cohen IR, Altmann DM: The role of hsp60 in autoimmume diabetes: analysis in a transgenic model. Proc Natl Acad Sci USA 93:1032-1037, 1996 (15.) Cohen IR: Treatment of autoimmune disease: to activate or to deactivate. Chem Immunol 60:150-160, 1995 (16.) Cohen IR: The cognitive principle challenges clonal selection. Immunol Today 13:441-444, 1992 (17.) Cohen IR: The cognitive paradigm and the immumological homunculus. Immunol Today 13:490-494, 1992

From the Department of Cell Biology, the Weizmann Institute of Science, Rehovot, Israel.

Address correspondence and reprint requests to Irun R. Cohen, The Department of Immunology, The Weizmann Institute of Science, Rehovot 7G100. Israel.

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I.R.C. is the incumbent of the Mauerberger Chair in Immunology and the director of the Robert Koch-Miner; a Center for Research in Autoimmune

Disease.

ELISA, enzyme-linked immunosorbent assay hsp60, 60-kDa heat shock protein IFA, incomplete Freund's adjuvant; IFN, interferon; IL, interleukin: OD, optical density; PBS. phosphate-buffered saline: STZ, streptozotocin: SI, stimulation index; TGF, transforming growth factor.

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SPECIAL FEATURES: illustration; graph
DESCRIPTORS: Diabetes--Prevention; Autoimmune diseases--Prevention; Peptides--Physiological aspects
FILE SEGMENT: HI File 149

14/9/5 (Item 2 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01497540 SUPPLIER NUMBER: 15981856 (THIS IS THE FULL TEXT)
Immunization with the larger isoform of mouse glutamic acid decarboxylase (GAD67) prevents autoimmune diabetes in NOD mice. (non-obese diabetic mice)
Elliott, John F.; Qin, Hui-Yu; Bhatti, Sunita; Smith, Dean K.; Singh, Raj Kumari; Dillon, Tom; Lauzon, Jana; Singh, Bhagirath
Diabetes, v43, n12, p1494(6)
Dec, 1994
PUBLICATION FORMAT: Magazine/Journal ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 5036 LINE COUNT: 00414

TEXT:

The 65-kDa isoform of glutamic acid decarboxylase ([GAD.sub.65]) has been implicated in autoimmune diabetes in NOD mice, but the role of the 67-kDa GAD isoform ([GAD.sub.67]) is less clear. We found that immunization of 4-week-old NOD mice with purified recombinant mouse [GAD.sub.67] prevented or significantly delayed the onset of diabetes. To further explore this phenomenon, we characterized anti-[GAD.sub.67] immune responses to naive and GAD-immunized NOD mice. Anti-[GAD.sub.67] antibodies titers were relatively low in naive mice at all ages, but a single immunization with [GAD.sub.67] at 4 weeks induced high titers of anti-GAD antibodies by 6 weeks of age. In both 4-week-old and diabetic NOD mice, there were significant endogenous T-cell proliferative responses against purified recombinant mouse [GAD.sub.67]. These T-cell proliferative responses were blocked by anti-I-[A.sup.NOD] and anti-CD4 antibodies. To characterize the anti-GAD T-cell responses in the NOD mice, we established T-cells lines and T-cell clones which recognized [GAD.sub.67], and we used recombinant subfragments of GAD to localize the predominant T-cell epitopes in [GAD.sub.67]. T-cells from naive NOD mice proliferated in response to all GAD subfragments, whereas T-cells from diabetic mice responded primarily to the COOH-terminal 83 amino acids of [GAD.sub.67]. These results suggest that [GAD.sub.67] is an autoantigen in IDDM and immunization of prediabetic NOD mice with [GAD.sub.67] can prevent the onset of diabetes. Diabetes 43:1494-1499, 1994

Insulin-dependent diabetes mellitus (IDDM) is an autoimmune disease that results from the destruction of insulin-producing [Beta]-cells in the islets of Langerhans[1]. This destruction is manifested by mononuclear cell infiltrates and a chronic inflammatory process in the islets of genetically predisposed individuals[2]. The selective destruction of [Beta]-cells is probably associated with autoantigens that for some unknown reason become

the target for immune recognition[3]. Antibodies to islet-associated antigens are present before the onset of IDDM; they include anti-islet cell antibodies, anti-insulin autoantibodies[2,3], antibodies to carboxypeptidase-H[4], antibodies to a 69-kDa protein possibly related to bovine serum albumin[5], and antibodies to a 64-kDa islet protein[6,7]. In humans, this 64-kDa autoantigen has been shown to be immunologically indistinguishable from the 65-kDa isoform of glutamic acid decarboxylase ([GAD.sub.65])[6,7].

GAD catalyzes the synthesis of the inhibitory neurotransmitter [gamma]-aminobutyric acid (GABA), and in the mammalian central nervous system it exists in two isomeric forms, [GAD.sub.65] and [GAD.sub.67][8]. Whereas rat and human pancreatic islets express [GAD.sub.65] predominantly or exclusively[9,10], mouse islets express both [GAD.sub.65] and [GAD.sub.67], and [GAD.sub.67] appears to predominate[11]. In human diabetic patients, if anti-GAD autoantibodies are present, they appear to be primarily against the [GAD.sub.65] isoform[7,10]. Autoantibodies to GAD have also been reported in BB rats and in NOD mice[12,13], although the GAD isoforms that are predominantly recognized in these animal models remain to be determined.

Both the [GAD.sub.65] and [GAD.sub.67] cDNAs have been cloned from rat[14] and human[15] brain, and the [GAD.sub.65] cDNAs have also been cloned from rat[16] and human[17] islets. The cDNA encoding mouse brain [GAD.sub.67] has been known for some time[18], ana more recently mouse [GAD.sub.65] has also been characterized[19]. GAD from cat brain[20] and Drosophila[21] have also been cloned. The availability of these cloned genes has made it possible to produce relatively large quantities of recombinant GAD in Escherichia coli or other expression systems. However, despite the fact that [GAD.sub.67] is the predominant isoform found in mouse islets, most immunological characterization in NOD mice has thus far focused on [GAD.sub.65]. In this study we characterize the endogenous and induced immune responses against [GAD.sub.67] in NOD mice.

RESEARCH DESIGN AND METHODS

NOD/Alt mice were obtained from the University of Alberta breeding colony, where the incidence of diabetes in female NOD mice is 80% by 20 weeks of age.

Antibodies. For antibody-blocking experiments, anti-CD4 (GK1.5) hybridoma supernatants were purified by ammonium sulfate precipitation (50%); dilutions were made from a 250 [mu]g/ml stock of salt-cut dialyzed protein. Anti-I-[A.sup.NOD] antibody (10.2.16) was added as ascites fluid at the dilutions indicated[22].

Cloning and expression of recombinant GAD and GAD subfragments. The cDNA clone 1A1, which encodes mouse [GAD.sub.67], was obtained from R. Greenspan (Roche Institute of Molecular Biology, Nutley, NJ). DNA sequencing of the 3' end of the 1A1 clone showed that the sequence was slightly different from that originally reported by Katarova et al.[18]. The specific changes were: insertion of a single G after nucleotide 1775, substitution of T for A at 1777, substitution of A for T at 1778, substitution of A for T at 1837, substitution of T for C at 1862, and substitution of T for C at 1863 (nucleotide numbering is the sanie as in Katarova et al.). These changes cause a shift in the reading frame and indicate that the true COOH terminus of mouse [GAD.sub.67] is different from that originally reported[18], but highly similar in sequence to that of [GAD.sub.65] and [GAD.sub.67] from a number of species[17].

The expression plasmid pT7-7 was obtained from S. Tabor, Harvard University (Cambridge, MA). The DNA sequence of the pT7-7 polylinker was determined to be [5'CATATGGCTAGAATTCGCGCCCGGGGATC CTCTAGAGTCGACCTGCAGCCCAAGCTTATCGATGATAAGCTGTCAA ACATGA-3'!, with translation beginning at the 5' most ATG. We constructed the expression

plasmid pT7-7His6 by adding the sequence [5'-CATATGCACCACCACCACCACCACCTGGTTCCGCGTGGTTCCGGA ATTC-3'! between the Nde I and Eco RI sites of the polylinker, using standard cloning methods[23]. The cDNA clone 1A1 was digested with Eco RI, and

5 ng of this material was amplified through 25 cycles of polymerase chain reaction in the presence of the primers 5'ATATATGA ATTCGCGCCATGGCATCTTCCACTCCTTC3' (5' primer) and 5'CT CTCTAAGCTTTTACAGATCCTGACCCAACCTCTC3'(3' primer). The resulting

1,800-base pair fragment was gel-purified, digested with Eco RI and Hin dIII, and ligated into pT7-7His6, which had been previously digested with the same enzymes. The protein expressed by this construct is referred to as MG1H. It is identical to mouse [GAD.sub.67], except that the sequence MHHHHHHLVPRGSGIRA has been added to the [NH.sub.2]-terminus (Fig. 5). The six histidine residues followed by a thrombin cleavage site allow for affinity purification over a nickelchelating column under denaturing conditions. Recombinant [GAD.sub.67] subfragments were engineered using a similar polymerase chain reaction strategy.

To express the recombinant proteins we transfected the corresponding plasmid into E. coli BL21/DE3[24] and grew several fresh colonies in individual small-scale cultures to test for protein expression. For larger scale expression, 1-liter cultures in 2 x yeast tryptone[23], 100 [mu]g/ml ampicillin, 0.2 mmol/l pyridoxal phosphate were grown in an air shaker at 37[degrees]C to an [OD.sub.600] of 0.6-0.8, and then induced with 0.4 mmol/l isopropyl-1-thio-[Beta]-D-galactopyranoside and grown for a further 3-4 h. Cells were collected by centrifugation (2,200 g, 4[degrees]C, 30 min), and the cell pellets were drained and resuspended in TPB (10 mmol/l Tris-HCl and 100 mmol/l phosphate buffer, pH 8.0; [tilde]20 ml/l of original culture). RNase A (2 [mu]g/ml), DNase (4 [mu]g/ml), and phenylmethylsulfonyl fluoride (1 mmol/l) (all reagents from Sigma, St. Louis, MO) were added and the cells were opened by passing them twice through a French press (16,000 psi). The bacterial extracts were centrifuged at 5,000 g at 4[degrees]C for 30 min to pellet the insoluble inclusion bodies, and peuets were resuspended in TPB (pH 8.0) and 6 mol/l guanidine HCl.

The recombinant proteins were purified by affinity chromatography over a nickel-chelating column and elution in 8 mol/l urea and TPB at low pH as described by Hochuli et al.[25]. The recombinant GAD proteins eluted at pH 5.0 and 4.5. These eluates were collected in fractions, and each fraction was analyzed by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE). Fractions containing the recombinant protein were pooled and then dialyzed at 4[degrees]C against SDS-PAGE running buffer (0.1% SDS)[23] for 24 h, SDS-PAGE running buffer (0.01% SDS) for 24 h, 4 mmol/l HEPES (pH 7.4) for 24 h, and finally 4 mmol/l HEPES (pH 7.4), 0.05 mmol/l pyridoxal phosphate for 24 h. The dialyzed material was lyophilized and stored as dry powder at -70[degrees]C. For immunological assays or immunizations, the lyophilized material was resuspended in phosphate-buffered saline (PBS) or RPMI-1640 at 1-2 mg/ml protein, sterilized by filtration (0.22 [mu]m), and stored at -20[degrees]C.

Immunization and monitoring for diabetes onset. Fifty microliters of purified recombinant [GAD.sub.67] (2 mg/ml in PBS) was emulsified with an equal volume of incomplete Freund's adjuvant (IFA) (GIBCO/BRL, Grand Island, NY), and the entire 100-[mu]l mixture was injected intraperitoneally into 4-week-old female NOD mice. Control mice received 50 [mu]l of IFA emulsified with 50 [mu]l of PBS alone. All mice were monitored biweekly for urine glucose using TES-TAPE I (Lilly, Indianapolis, IN). Once the urine tested positive for glucose, blood glucose levels were monitored daily using Glucoscan 2000 test strips (Lifescan, Milpitas, CA). Mice were killed when blood glucose levels rose above 16.7 mmol/l on 2 consecutive

days.

Measurement of anti-GAD antibodies by enzyme-linked immunosorbent assay (ELISA). Flat-bottomed 96-well plates (Pro-Bind; Falcon, Oxnard, CA) were coated with recombinant purified [GAD.sub.67] (10 Kg protein/ird in 0.2 mol/l Tris-HCl, pH 7.2; 50 [mu]l/well) by incubating overnight at 4[degrees]C. The ELISA assay was performed using standard methods, and results are presented as absorbance at 405 nm, recorded by using a Molecular Devices [UV.sub.max] kinetic microplate reader.

T-cell proliferation assays. Single cell suspensions of cells were obtained from the spleen or lymph nodes as described[26], and erythrocytes were lysed by incubation for 2 min at 18[degrees]C in a solution of Tris-HCl (170 mmol/l), pH 7.2) and [NH.sub.4]Cl (0.83% wt/vol). The cells were washed, resuspended in complete RPMI media (RPMI-1640, 100 [mu]g/ml gentamycin, 10 mmol/l HEPES, [10.sup.-5] mmol/l 2-mercaptoethanol, and 10% fetal calf serum), and a nylon wool column used to enrich for T-lymphocytes as described[27]. The column and cells were incubated 1 h at 37[degrees]C, and nonadherent cells were collected by washing the column with several volumes of complete RPMI (prewarmed to 37[degrees]C); 3,000 rad irradiated spleen cells were used as antigen-presenting cells (APCs). T-cell proliferation assays were done in flat-bottomed 96-well plates using complete RPMI media (200 [mu]l/well) with varying amounts of antigen, 2 x [10.sup.5] bulk T-lymphocytes, and 4-5 x [10.sup.5] APCs added per well. The cultures were incubated for 80 h, then pulsed with [[methyl-.sup.3]H] thymidine (1 [mu]Ci/well; Du Pont-NEN, Boston, MA), harvested onto glass fiber filters 16 h later, and counted in a scintillation counter.

GAD reactive T-cell lines and clones. To establish T-cell lines, NOD mice were immunized in the hind footpad with 100 [mu]l mouse [GAD.sub.67] in IFA (1.0 mg/ml [GAD.sub.67] in PBS emulsified with an equal volume of IFA). Ten days later the draining popliteal lymph node was removed, and nylon wool-enriched T-cells were prepared and plated out in 96-well flat-bottomed plates (4 x [10.sup.5] T-cells/ml; 200 [mu]l/well). Cultures were stimulated with mouse [GAD.sub.67] (20 [mu]g/ml) in the presence of 3,000 rad irradiated syngeneic spleen cells (1 x [10.sup.6] cells/well). After 5 days, cells were transferred to 24-well plates and incubation was continued in the presence of a 1:100 dilution of rat interleukin-2 (IL-2) (natural rat interleukin-2, partialy purified, from Collaborative Research, Bedford, MA). Seven to 10 days later, live cells were purified by centrifugation over Lympholyte-M (Cederlane, Hornby, Ontario, Canada), and antigen specificity was tested using the standard proliferation assay described above (20 [mu]g/ml [GAD.sub.67]). Antigen-specific cell lines were expanded using alternating cycles of stimulation with [GAD.sub.67] and irradiated APCs (5 days of culture with 20 [mu]g/ml GAD67 and 1 x [10.sup.6] APCs/well), followed by stimulation with rat IL-2 (10 days of culture with 1:100 dilution).

T-cell clones were established from the antigen-specific [GAD.sub.67]-reactive T-cell lines by the limiting dilution method. Cells were plated in 96-well plates (0.3 cells/well) in the presence of irradiated syngeneic spleen cells (5 x [10.sub.5] cells/well), [GAD.sub.67] (20 [mu]g/ml), and rat IL-2 (1:100 dilution in RPMI-1640). Ten to 15 days later, cloned T-cells were transferred into 24-well plates and expanded using alternating cycles of stimulation with [GAD.sub.67] and irradiated APCs (5 days of culture with 20 [mu]g/ml [GAD.sub.67] and 5 x [10.sup.5] APCs/well), followed by stimulation with rat IL-2 (10 days of culture with 1:100 dilution). To demonstrate antigen specificity, cloned 7-cells (1 x [10.sup.4] cells/well) were incubated with irradiated syngeneic spleen cells (5 x [10.sup.5] cells/well) and [GAD.sub.67] (20 [mug/ml), and proliferation was measured after 96 h.

RESULTS

SDS-PAGE analysis of purified GAD antigens. Recombinant mouse [GAD.sub.67] was purified as described under METHODS,

5 [mu]g of purified protein was separated on SDS-PAGE, and the gel was stained with Coomassie blue. A single predominant band of the expected size was observed (Fig. 1).

Administration of mouse GAD67 prevents NOD mice from developing spontaneous diabetes. To detemine what effect the deliberate induction of anti-[GAD.sub.67] immune responses would have on the onset of diabetes, we immunized 4-week-old female NOD mice with purified [GAD.sub.67] in IFA and followed them for the onset of hyperglycemia. In preliminary experiments (data not shown), five IFA-immunized control mice became diabetic by 20 weeks, whereas five [GAD.sub.67]-immunized mice remained diabetes free for >35 weeks. This experiment was repeated with 10 to 15 mice/group, and the results are shown in Fig. 2. In this case, three of the IFA-immunized mice and all of the [GAD.sub.67]-immunized mice remained diabetes free for >35 weeks.

A single immunization with mouse [GAD.sub.67] induces anti-GAD antibodies. Using purified recombinant mouse [GAD.sub.67], we established an ELISA that could be used to measure titers of anti-mouse GAD antibodies. We found minimal levels of anti-GAD antibodies in 6-week-old naive NOD mice, and titers were essentially the same in diabetic mice. In contrast, in mice immunized with mouse [GAD.sub.67] at 4 weeks of age, antibody titers were increased at least 30-fold by 6 weeks of age (Fig. 3).

NOD T-lymphocytes proliferate in response to mouse [GAD.sub.67], and this proliferation is blocked by anti-I-A and anti-CD4 antibodies. T-lymphocytes were purified from the lymph nodes of prediabetic (6-week-old) and diabetic female NOD mice, mixed with irradiated spleen cells as APCs, and cultured in the presence of recombinant mouse [GAD.sub.67]. At both ages, a strong anti-[GAD.sub.67] Proliferative response was seen, and in both cases this proliferation could be blocked by either anti-I-[A.sup.NOD] or anti-CD4 antibodies (Fig. 4).

NOD T-cell lines and clones that recognize recombinant mouse [GAD.sub.67]. We raised T-cell lines by stimulating NOD T-lymphocytes repeatedly with purified recombinant mouse [GAD.sub.67] in the presence of APCs. Two independent T-cell lines, ML1 and ML3, were established. Both showed strong proliferative responses to mouse [GAD.sub.67] (Table 1). Using the same antigen preparation on limiting dilution cultures, we raised two GAD-reactive T-cell clones, M3.3 and M3.5 (Table 2). These clones proliferate in response to recombinant mouse [GAD.sub.67] and APCs but do not show significant proliferative response to an unrelated recombinant malaria antigen preparation (PfsY-C1), which was expressed and purified in an identical fashion as the recombinant [GAD.sub.67].

[TABULAR DATA OMITTED]

T-cell proliferative responses to recombinant subfragments of mouse [GAD.sub.67]. To better define the region of mouse [GAD.sub.67] that is recognized by NOD T-lymphocytes, we expressed and purified the subfragments of the protein shown in Fig. 5. Bulk splenic T-cells from 6-week-old mice appeared to recognize all four [GAD.sub.67] subfragments, although subfragments 2 and 5 give the strongest proliferative response (Fig. 6A). In contrast, splenic T-cells from diabetic mice appear to have a much stronger proliferative response to subfragment 5, and the proliferative responses to the other subfragments are correspondingly diminished.

DISCUSSION

Since [GAD.sub.67] appears to be the predominant GAD isoform expressed in mouse islets (11), we assumed that it would be a major target of the autoimmune response in NOD mice. This assumption is supported by thé work of Tisch et al.[28], who showed that prediabetic NOD mice have T-cell responses against both mouse GAD isoforms. Kaufman et al.[29] have shown

that immunization of young NOD mice with human [GAD.sub.65], can prevent diabetes, but we were interested to know if mouse [GAD.sub.67] would have a similar effect. If, for example, [GAD.sub.67] failed to protect, it would suggest a relatively unique role for [GAD.sub.65] in the autoimmune process. Our preliminary results suggested that immunization with [GAD.sub.67] also has a protective effect, and subsequent experiments using a larger number of animals confirmed this observation. This implicates [GAD.sub.67] in the autoimmune process in NOD mice and led us to investigate the nature of the antibody and T-cell responses against [GAD.sub.67] in the naive and GAD-immunized animals.

Naive NOD mice had minimal titers of anti-[GAD.sub.67] antibodies, and these increased only slightly as the niice aged. In contrast, but perhaps not unexpectedly, in mice that were inununized with a single dose of mouse [GAD.sub.67] in IFA, the titers of anti-mouse GAD67 antibodies rose significantly within a few weeks (Fig. 2).

In contrast to antibody responses, both 4-week-old and diabetic NOD mice had significant endogenous T-cell proliferative responses against purified recombinant mouse [GAD.sub.67]. To further characterize the proliferating cell populations, we incubated purified T-cells, antigen, and irradiated APCs in the presence of two different blocking monoclonal antibodies (Fig. 4). Inhibition by the anti-I-[A.sup.NOD] monoclonal antibody suggests that presentation of the GAD antigen via class II molecules is required to stimulate the majority of the [GAD.sub.67]-reactive T-cells. Furthermore, many of the proliferating T-cells are [CD4.sup.+], because the anti-CD4 appears to consistently reduce prouferation to roughly the same levels as seen with the anti-class H antibody.

Although the [GAD.sub.67] used in our T-cell proliferation assays was highly purified (Fig. 1), the antigen preparation could potentially contain additional mitogenic agents. Such agents would stimulate lymphocyte proliferation (T- and/or B-lymphocytes) in a nonspecific manner that would be independent of antigen presentation. However, the fact that T-cells from other strains of mice did not proliferate in response to the GAD preparation (data not shown), together with the observation that the NOD T-cell proliferative responses are significantly blocked by anti-I-[A.sup.NOD], supports the idea that this response is antigen-specific and that it requires the presentation of GAD peptides by NOD class II molecules.

To further characterize the anti-[GAD.sub.67] T-cell response, we have developed GAD specific T-cell lines and clones (Tables 1 and 2). The fact that such lines and clones can be established provides additional evidence that T-cells which recognize [GAD.sub.67] exist within the NOD inimune system. These [GAD.sub.67] reactive T-cell lines and clones can now be used to map T-cell epitopes within [GAD.sub.67].

Rather than mouse [GAD.sub.67], it is possible that some contaminating bacterial protein in the antigen preparation might be presented on NOD class II molecules and induce proliferation of the T-cell clones M3.3 and M3.5. To exclude this possibility, we tested the clones for proliferative response to an unrelated recombinant malarial antigen, PfsY-Cl. This malaria antigen has the same [NH.sub.2]-terminal Met[(His).sub.6] and thrombin cleavage site as the recombinant mouse [GAD.sub.67] molecules (see Fig. 5 legend), and it was expressed in the same bacterial host and purified over a nickel-chelating column using identical conditions as for the recombinant GAD antigen preparations. Thus, any nonspecific bacterial contaminants that are present in the recombinant [GAD.sub.67] would also be present in the PfsY-C1 antigen preparation. However, the malaria antigen did not stimulate proliferation of the [GAD.sub.67] reactive T-cell lines (data not shown) or clones (Table 2).

[TABULAR DATA OMITTED]

To delineate the predominant T-cell epitopes in [GAD.sub.67], we made and purified subfragments of mouse [GAD.sub.67] (Fig. 5) and used the various purified polypeptides in a proliferation assay with nylon wool-enriched splenic T-cells from 6-week-old and diabetic NOD ntice (Flg. 6). These results suggest that whereas 6-week-old mice see a variety of epitopes on [GAD.sub.67], as the animals progress to diabetes the immune response appears to be increasingly limited to fragment 5, which contains residues 400-585 of [GAD.sub.67]. However, because the same cells do not respond to fragment 4, which includes residues 300-502, this would suggest that the major T-cell epitope is limited to the COOH-terminal 83 amino acids of [GAD.sub.67].

A limited number of specific peptides derived from the human [GAD.sub.65] protein have recently been shown to stimulate the proliferation of splenic T-cells from young prediabetic NOD mice[29], and these peptides are thought to embody the predominant and earliest T-cell determinants of [GAD.sub.65] recognized by the NOD immune system. These peptides come largely from near the COOH terminus of human [GAD.sub.65], and a highly similar sequence occurs in the COOH-terminal region of mouse [GAD.sub.67], with the corresponding peptide elements found entirely within the COOH-terminal 83 amino acids of [GAD.sub.67]. However, the findings of Kaufman et al.[29] using the set of overlapping human [GAD.sub.65] peptides suggest that T-cells from young NOD mice initially recognize a limited region of [GAD.sub.65] and that as the autoimmune response progresses, the NOD inimune system recognizes an increasing number of different peptide elements derived from [GAD.sub.65]. In contrast, our results suggest that as the autoimmune response progresses, an increasing proportion of the GAD-reactive T-cells recognize a limited subsegment of [GAD.sub.67], which lies within the COOH-terminal 83 amino acids of the molecule.

Given that immunization with mouse [GAD.sub.67] appeared to delay the onset of diabetes in NOD mice, it is interesting to consider exactly how the existing endogenous anti-GAD immune response may have been altered by the immunization. It is likely that the subset of T-cells that are induced by GAD immunization are of T-helper 2 (TH2) type and these cells block the potentially autoreactive T-helper 1 (TH1) type cells. This may be similar to what might happen when NOD mice are protected from IDDM by immunostimulation with adjuvants such as CFA[30]. In terms of subclasses of T-cell responses[31], we have not yet carried out a detailed analysis of the differences between the GAD-reactive T-cells from our GAD-immunized (i.e., protected) mice and our nonimmunized (i.e., susceptible) mice. From our existing data we can say that the anti-GAD antibody titers are much higher in the immunized mice than in the nonimmunized animals, and this may reflect a shift in anti-GAD T-cell immune responses toward a TH2-like response in the immunized group. This idea is at least consistent with the finding that in normal (i.e., unimmunized, prediabetic) NOD mice, the endogenous anti-mouse GAD T-cell response is essentially TH1-like[29]. Our results suggest potential immunotherapy of autoimmune diseases such as IDDM by immunization with relevant autoantigens that could alter the ratio of subset T-helper-cell subset.

REFERENCES

[1.] Cooke A: An overview on possible mechanisnis of destruction of the insulin-producing beta cell. Curr Topics Microbiol Immunol 164:125-142, 1990 [2.] Castano L, Eisenbarth GS: Type-I diabetes: a chronic autoimmune disease of human, mouse, and rat. Annu Rev Immunol 8:647-679, 1990 [3.] Harrison LC: Islet cell antigens in insulin-dependent diabetes: Pandora's box revisited. Immunol Today 13:348-352, 1992 [4.] Castano L, Russo E, Zhou L, Lipes MA, Eisenbarth GS: Identification and cloning of a granule autoantigen (carboxypeptidase-H) associated with type I diabetes. J Clin

Endrocrinol Metab 73:1197-1201, 1991 [5.] Karjalainen J, Martin JM, Knip M, Ionen J, Robinson BH, Savilahti E, Akerblom HK, Dosch H: A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus. N Engl J Med 327:302-307, 1992 [6.] Baekkeskov S, Warnock G, Christie M, Rajotte RV, Larsen PM, Fey S: Revelation of specificity of 64K autoantibodies in IDDM serums by high-resolution 2-D gel electrophoresis: unambiguous identification of 64K target antigen. Diabetes 38:1133-1141, 1989 [7.] Baekkeskov S, Aanstoot HJ, Christgau S: Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Natum 347:151-156, 1990 (Published erratum appears in Nature 347:782, 1990) [8.] Erlander MG, Tobin AJ: The structural and functional heterogeneity of glutamic acid decarboxylase: a review. Neurochem Res 16:215-226, 1991 [9.] Karlsen AE, Hagopian WA, Petersen JS, Boel E, Dyrberg T, Grunin CE, Michelsen BK, Madsen OD, Lernmark A: Recombinant glutamic acid decarboxylase (representing the single isoform expressed in human islets) detects IDDM-associated 64,000-[M.sub.r] autoantibodies. Diabetes 41: 1355-1359,1992 [10.] Hagopian WA, Michelsen B, Karlsen AE, Larsen F, Moody A, Grubin DC, Rowe R, Petersen J, McEvoy R, Lernmark A: Autoantibodies in IDDM primarily recognize the 65,000-[M.sub.r] rather than the 67,000-[M.sub.r] isoform of glutamic acid decarboxylase. Diabetes 42:631-636, 1993 [11.] Kim J, Richter W, Aanstoot H-J, Shi Y, Fu Q, Rojotte R, Warnock G, Baekkeskov S: Differential expression of [GAD.sub.65] and [GAD.sub.7] in pancreatic islets of man, rat, and mouse. Diabetes 42:1799-1808, 1993 [12.] Baekkeskov S, Dyrberg T, Lernmark A: Autoantibodies to a 64-kilodalton islet cell protein precede the onset of spontaneous diabetes in the BB rat. Science 224:1348-1350, 1984 [13.] Atkinson MA, Maclaren NK: Autoantibodies in nonobese diabetic mice immunoprecipitate 64,000-[M.sub.r] islet antigen. Diabetes 37:1587-1590, 1988 [14.] Erlander MG, Tilakaratne NJ, Feldblum S, Patel N, Tobin AJ: Two genes encode distinct glutamate decarboxylases. Neuron 7:91-100, 1991 [15.] Bu D, Erlander MG, Hitz BC, Tilakaratne NJ, Kaufman DL, Wagner-McPherson CB, Evans GA, Tobin AJ: Two human glutamate decarboxylases, 65-kDa GAD and 67-kDa GAD, are each encoded by a single gene. Proc Natl Acad Sci USA 89:2115-2119, 1992 [16.] Michelsen BK, Petersen JS, Boel E, Moldrup A, Dyrberg T, Madsen OD: Cloning, characterization, and autoimmune recognition of rat islet glutamic acid decarboxylase in insulin-dependent diabetes mellitus. Proc Natl Acad Sci USA 88:8754-8758, 1991 [17.] Karlsen AE, Hagopian WA, Grubin CE, Dube S, Disteche CM, Adler DA, Barmeier H, Mathewes S, Grant FJ, Foster D, Lernmark A: Cloning and primary structure of a human islet isoform of glutamic acid decarboxylase from chromosome 10. Proc Natl Acad Sci USA 88:8337-8341, 1991 [18.] Katarova Z, Szabo G, Mugnaini E, Greenspan RJ: Molecular identification of the 62 kd form of glutamic acid decarboxylase from the mouse. Eur J Neurosci 2:190-202, 1990 [19.] Lee DS, Tian J, Phan T, Kaufman DL: Cloning and sequence analysis of a murine cDNA encoding glutamate decarboxylase (GAD65). Biochim Biophys Acta 1216:157-160, 1993 [20.] Kobayashi Y, Kaufman DL, Tobin AJ: Glutamic acid decarboxylase cDNA nucleotide sequence encoding an enzymatically active fusion protein. J Neurosci 7:2768-2772, 1987 [21.] Jackson FR, Newby LM, Kulkarni SJ: Drosophila GABAergic systems sequence and expression of glutamic acid decarboxylase. J Neurochem 54:1068-1078, 1990 [22.] Singh B, Dillon T, Fraga E, Lauzon J: Role of the first external domain of I-A beta chain m mimune responses and diabetes in non-obese diabetic (NOD) mice. J Autoimmun 3:507-521, 1990 [23.] Sambrook J, Fritsch EF, Maniatis T: Molecular Cloning: A Laboratory Manual. 2nd ed. Cold Spring Harbor, NY, Cold Spring Harbor Press, 1989 [24.] Studier FW, Rosenberg AH, Dunn JJ, Dubendorff JW: Use of T7 RNA polymerase to direct expression of cloned genes. Methods Enzymol 185:60-89, 1990 [25.] Hochuli E, Bannworth W, Dobeli H, Gentz R, Stuber D: Genetic approach to facilitate purification of

recombinant proteins with a novel metal chelate adsorbent Bio/Technology 6:1321-1325, 1988 [26.] Fotedar A, Boyer M, Smart W, Widtman J, Fraga E, Singh B: Fine specificity of antigen recognition by T cell hybridoma clones specific for poly-18. a synthetic polypeptide antigen of defined sequence and conformation. J Immunol 135:3028-3033, 1985 [27.] Fotedar A, Smart W, Boyer M, Dillon T, Fraga E, Lauzon J, Shevach EM, Singh B: Characterization of agretopes and epitopes involved in the presentation of beef insulin to T cells. Mol Immunol 27:603-611, 1990 [28.] Tisch R, Yang X-D, Singer SM, Liblau RS, Fugger L, McDevin HO: Immune response to glutamic acid decarboxylase correlates with insulitis in non-obese diabetic mice. Nature 366:72-75, 1993 [29.] Kaufman DL, Clare-Salzler M, Tian J, Forstuber T, Ting GS, Robinson P, Atkinson MA, Sercarz EE, Tobin AJ, Lehmann PV: Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. Nature 366:69-72, 1993 [30.] Qin HY, Sadelain MWJ, Hitchon C, Lauzon J, Singh B: Complete Freund's adjuvant-induced T cells prevent the development and adoptive transfer of diabetes in nonobese diabetic mice. J Immunol 150:2072-2080, 1993 [31.] Powrie F, Coffman RL- Cytokine regulation of T-cell function: potential for therapeutic intervention. Immunol Today 14:270-274, 1993
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The 12th International Immunology of Diabetes Workshop was held during April 1993 in Orlando, Florida, to review research progress since the 11th Immunology of Diabetes Workshop meeting in Nagasaki, Japan, one and a half years before. The NOD mouse may have as many as 10 susceptibility genes, including its novel IA major histocompatibility complex antigen and a defective interferon-[gamma] receptor, whereas human IDDM is so far known to be encoded by cis and trans complementation products of certain DQ genes on chromosome 6q, and a gene in the insulin-like growth factor II region on chromosome 11p. A unique protein regulator of the X box promotor of the highly susceptible DQB*0302 allele has also been found. Islet cell antibody negative siblings of IDDM patients appear to have lower than expected abilities to secrete insulin in response to intravenous glucose. Sera from patients before and/or after developing IDDM immunoprecipitate two native proteins of 64,000- and 38,000-[M.sub.r] glutamic acid decarboxylase ([GAD.sub.65]) reacting to conformational epitopes. However, a multitude of other autoantibodies often reacting to denatured proteins through linear epitopes have also been identified. The

first workshop for GAD antibody assays was successfully completed; however, the 38,000-[M.sup.r] antigen has not yet been identified. Other autoantibodies reactive to gangliosides and to sulfatides continue to be reported. Insulitis has come to be recognized as a sometimes protective event. Protective insulitis predominates in older lesions. It can be induced by as disparate means as tuberculin antigen administration, by interleukin-4 treatments, by transfer of T-cell lines generated in autologous mixed lmphocyte responses, and by immunization to insulin B-chain, whereas oral islet cell antigens, such as insulin, can delay diabetes onset in the NOD mouse. Although Th2 cells may be important in protective insulitis, the NOD may actually have a deficiency of Th1 cells. Encapsulated islets can function for months after transplantation, whereas xenogeneic islet grafts appear to be rejected through a [CD4.sup.+] T-cell--mediated mechanism like the pathogenic destruction of islets seen in NOD mice. We summarize a few of the meeting highlights. Diabetes 42:1099-104, 1993

The first research meeting devoted to the immunology of diabetes was convened in 1976 in Philadelphia under the auspices of the JDF. Some 30 participants from Europe and the U.S. were involved. Islet cell autoantibodies had just been established as characteristic of IDDM patients, a finding that documented the autoimmune nature of the disease. This past April 1993, the 12th International Immunology and Diabetes Workshop was held in Orlando, Florida, under sponsorship of the ADA. More than 350 participants from many countries of the world presented their most recent research findings as relevant to the underlying genetics, pathogenesis, predictability, and eventual prevention of the disease. Progress in islet cell and pancreatic transplantation was a new feature of this meeting. We present a synopsis of the meeting emphasizing areas that proved to be the most active foci for discussion and enlightenment.

TABLE 1

IDDM and its genes

Candidate gene	Species	Chromosome
Class II MHC		
DQA/DQB complementation	Human	6
Regulator X box DQB*0302	Human	6
? TAP2 (transporter gene)	Human	6
IA[Beta]	NOD mouse	17
Others		
High affinity [F.sub.c] receptor	NOD mouse	3 telomeric
?IL-2	NOD mouse	3 centromeric
INF-[gamma] receptor	NOD mouse	10
Insulin/IGF-II	Human	11
Known genomic intervals	NOD mouse	1, 2, 3, 6, 11, 15

GENETICS

Acknowledging the inherent difficulties in studying diverse outbred human populations to locate the susceptibility genes of IDDM, numerous groups studied the NOD mouse hoping to gain insights that could apply to humans. Using a variety of strategies to link microsatellite-based genomic intervals and candidate genes to the occurrence of insulitis and diabetes in a number of NOD cross-bred mice, as many as 10 separate relevant loci were identified. The most important of these were the class II antigens of the MHC on chromosome 17 and two distinct loci found on chromosome 3. The candidate genes involved are the IA locus within the MHC, the structural gene for IL-2, and the high affinity [F.sub.c] receptor gene for IgG (Table 1).

The predisposition to an inflammatory infiltrate within the pancreatic islets (insulitis) in some cases was distinct from that of diabetes. This could be seen for loci on chromosomes 1 and 3 in particular.

Other suggested loci were mapped to chrosomes 6, 11, and 15, and resistance genes were preliminarily located on chromosomes 1, 2, 3, 5, and 18 in congenic and outbred strains of NOD mice. As is the case with some other normal mice, e.g., those of b and/or s MHC haplotypes, the NOD expresses only one class II MHC antigen, because of a regulatory genetic defect in the promoter region of the IE [alpha]-chain gene. In previous studies, it has been shown that when the NOD expresses IE [alpha]/[Beta]-dimeric molecules through the means of IE [alpha]-transgenes or through breeding NOD mice congenic for IE [alpha]-genes, diabetes does not result. The protection appears to be only relative because outbred NOD [IE.sup.+] and [IE.sup.-] cogenic mice developed late- onset diabetes equally well and could be shown to be susceptible to diabetes after adaptive transfer of splenocytes from NOD mice.

It has been established that the IA of the NOD is unique, resulting from a b/d haplotype recombinant event, and has a Ser in position 57 of the [beta]-chain instead of the more common Asp. The importance of the IA of NOD probably resides in its affinity to bind to a disease-specific islet cell peptide antigen because of particular motifs within its binding cleft. Thus, immune enhancement to the antigen or loss of immune tolerance might result. Similarly, the BB rat requires its U MHC haplotype for diabetes susceptibility, but 3 other recessive genes are thought to be involved as well. The BB lymphopenia gene has been mapped to a genomic segment close to the neuropeptide Y and carboxypeptidase genes. In humans with IDDM, only one gene, located 3' to the insulin gene and proximal to the IGF-II gene on chromosome 11 (INS locus), in addition to the HLA DR/DQ loci on chromosome 6, has been clearly identified to convey disease susceptibility.

Among Caucasians, DQ molecules that are cis and/or trans combinations of an [alpha]-chain with an Arg at position 52 and a [beta]-chain with an Ala at position 57 encode susceptibility to IDDM. Typically, these susceptibility alleles occur on DR3 (DQA1*0501/DQB1*0201) and DR4 (DQA1*0301/DQB1*0302) HLA haplotypes, and DQA1*0102/DQB1*0602 is dominantly protective. However, among Japanese, IDDM is associated with DR4, 8, and 9 but not DR3. In Japanese, the disease can be phenotypically divided into acute versus slowly progressive subtypes. Acute IDDM was found to be associated with two [DR4.sup.+] haplotypes, i.e., DQA1*0301/DQB1*0401 ([Asp.sup.+]) and DQA1*0301/DQB1*0302, and one [DR9.sup.+] haplotype, DQA1*0301/DQB1*0303, whereas slow-onset IDDM was only associated with DQA1*0301/DQB1*0401. Thus, among Japanese, IDDM susceptibility is most often actually encoded by HLA haplotypes with a residue [Asp.sup.+]57 DQB1; however, such haplotypes usually have an Arg [52.sup.+] DQA1 and an [Asp.sup.-]57 DRB1.

The case for a gender-related transmission bias for IDDM-associated HLA haplotypes continues to be inconclusive. However, a Danish report suggested that DQA1*0301/DQB1*0302 was preferentially passed from fathers and DQA1*0501/DQB1*0201 from mothers to affected offspring. Of great potential importance was the finding of specific regulator protein interactions with the X box associated uniquely with the DQB1*0302 gene. Thus, quantitative expression differences between IDDM-associated versus nonassociated class II HLA alleles might prove to be involved in the predisposition to IDDM. Another study has suggested that T-cell expression of class I MHC in IDDM patients as well as NOD mice is defective, albeit, this remains controversial. Thus, it was of interest that a negative association was reported with the peptide transporter 2 (TAP2) gene among French patients. Unfortunately, similar studies among Finnish, Norwegian, and Japanese patients found such TAP2 associations to be entirely secondary to linkage disequilibria with HLA-DQ/DR alleles already known to be linked to IDDM susceptibility.

Although the INS locus has limited polymorphisms, patients with IDDM

have increased rates of homozygosity for the common allele in both [DR4.sup.+] and [DR4.sup.-] patients. A complex interaction between the INS gene and DQ alleles appears possible, as does evidence for a paternal transmission bias for the IDDM-associated allele. The possibility of a maternal imprinting effect, where the maternal INS gene becomes inactivated, has been suggested but not proven. The presence of IAAs among nondiabetic relatives of individuals with IDDM has been reported to be associated with HLA-DR4, and the association may be strengthened by determination of the DQA1 alleles, according to one report. Interestingly patients with the Stiff Man Syndrome were found to have increased frequencies of DQB1*06 and DQB1*0201 alleles, with increases of the latter especially associated with coincident IDDM.

In summary, the search for the IDDM genes in humans is an active area for investigation. Those genomic intervals found to affect insulitis and/or diabetes in NOD mice may assist in the location of the human counterparts to genomic regions that have synteny, or similarities, in genetic composition. More likely, however, the identification of the actual candidate genes within genomic intervals in the NOD mouse may provide functional information that could lead to the indentification of similar dysfunctions in humans, most likely involving different underlying genetic lesions.

IMMUNOBIOLOGY

Although it is relatively easy to transfer disease to young NOD animals (<3 wk of age), it becomes increasingly more difficult to transfer disease as the recipient mice age. For this reason, disease transfer to older prediabetic mice requires irradiation beforehand. It was shown that development of the immune system in NOD animals involves the generation of both destructive T-cells as well as another set of T-cells that expresses the [CD4.sup.+] phenotype and negatively regulates the disease process. Disease transfer to nonirradiated animals is possible, provided these protective cells are eliminated by treatment of recipient NOD mice with anti-CD4 antibodies. In an interesting study, pancreatic [beta]-cells were destroyed in early life by ALX treatment. These studies demonstrated that the presence of active insulin-secreting [beta]-cells were required for the activation of the disease process. The self antigens expressed by these cells were seen to drive the autoimmune process leading to [beta]-cell destruction and diabetes. Thus, the disease could not be transferred from [beta]-cell -- depleted mice.

Although treatment of disease-prone NOD mice with nondepleting anti-CD4 antibodies protects NOD mice from their development of clinical disease, these animals still develop pancreatic insulitis. Such insulitis is nondestructive and is associated with the accumulation of lymphocytes in a peri-islet distribution. The mice, although protected from spontaneous diabetes, are still disease prone because diabetes can be rapidly precipitated after treatment with cyclophosphamide. Stimulation of the NOD immune system with CFA or BCG either early, or late (85 days) in the disease process also results in the development of nondestructive lesions in the pancreatic islets. These animals also can be shown to be disease prone, because diabetes can still be precipitated by cyclophosphamide treatment. In contrast, when NOD mice are protected by treatment with anti-class II antibody, diabetes cannot be induced by cyclophosphamide. These findings show that diabetes in the NOD mouse can be regulated by either immunostimulation or by immunosuppression. In most cases, the mice remain diabetes prone but develop nondestructive lesions in their pancreases. This negative regulation involves [CD4.sup.+] cells that can be negated by cyclophamide treatments.

The AMLR in NOD mice has been found to be defective by several investigators. Autoreactive [CD4.sup.+]TCR-[alpha]/[[beta].sup.+] T-cell

clones were developed in AMLR response to syngeneic antigen presenting cells, which on cotransfer experiments protected the animals from severe intra-islet insulitis and diabetes. These clones inhibited proliferation of T-cells responding to allogeneic stimulator cells without affecting IL-2 production. The inhibition was the result of growth arrest but not apoptosis of responder T-cells.

Whereas [CD4.sup.+] T-cells are of critical importance to regulation, the relative roles of [CD4.sup.+] and [CD8.sup.+] T-cells in the destruction of pancreatic [beta]-cells remains debatable. The findings of [beta]-cell--destructive [CD4.sup.+] T-cell clones clearly indicate the [CD4.sup.+] T-cell alone is sufficient for the transfer of insulitis and diabetes to NOD-scid mice. Some of the clones generated from the NOD insulitis lesions showed strong reactivities to insulin (procine and rat), indicating that insulin itself may be an autoantigen of importance in the disease. The [CD8.sup.+] T-cell, however, appears to be required for the initiation of the disease, albeit, the function of this cell remains one of the outstanding enigmas in disease pathogenesis.

In pancreatic biopsies taken from Japanese who developed IDDM, [CD8.sup.+] T-cells were the predominant cells in the islet infiltrates. Nevertheless, in adoptive transfer studies involving transgenic mice expressing influenza hemagglutinin on [beta]-cells, [CD4.sup.+]-cells and [F4/80.sup.+] macrophages dominated the early infiltrates, and in spontaneous diabetes in NOD mice, the lymphocytic infiltrates developed around a network of VCAM-[1.sup.+] [ICAM.sup.+] dendritic cells. In chimeric animals, insulitis and diabetes could occur even when the responding T-cells were unable to recognize islet-specific antigens directly on [beta]-cells, suggesting that direct contact between pathogenic [CD4.sup.+] T-cells and [beta]-cells is not required. TNF-[alpha], given to NOD mice from the neonatal period, accelerated diabetes development, whereas treatments with anti-TNF-[alpha] antibodies powerfully prevented diabetes. Treatments with IFN-[gamma], however, had no effects. These findings coincided with a report that IFN-[gamma] knock-out NOD mice have essentially normal rates of diabetes. Sequence analyses of peptides presented by the unique MHC class II molecules isolated from NON splenocytes also has been undertaken. Peptides from serum albumin, fibronectin, and ribonuclear proteins were eluted and sequenced. The serum albumin peptide demonstrated allele-specific binding to IA-NOD but not [IA.sup.b]. It remains to be seen whether this kind of approach will prove useful in identifying novel autoantigens in IDDM.

ISLET CELL ANTIGENS AND IDDM PREDICTION

The islet cell antigens that are targeted by the autoimmune process that leads to IDDM have been identified by T-cell or autoantibody reactivities. The number of putative islet autoantigens in IDDM has grown dramatically over the past 2-3 yr, demanding continued evaluation of their potential roles in the pathogenesis of the disease. When islet cells are metabolically labeled in vitro and their detergent lysates exposed to sera from patients with IDDM or from those who subsequently developed IDDM, only two protein antigens of 64,000 and 38,000 [M.sub.r] can be regularly immunoprecipitated. This suggests that these proteins must be in their native configuration and that the reactive epitopes are likely to be conformational in nature. Arguably, this would imply a greater likelihood for a primary pathogenic role for these autoantigens, because the formation of their respective autoantibodies might be expected to involve whole rather than denatured proteins if a T-cell response to them occurred as an inductive event in the disease (Table 2).

TABLE 2

Antigen highlights

[GAD.sub.65] antibody epitopes recognized: confirmational plus

linear
37,000/38,000 [M.sub.r]: unknown antigens not GAD fragments
Insulin-responsive T-cell lines: transfer diabetes/NOD-scid
Milk albumin-related ICA69 molecule: cloned and expressed
GM2-1 ganglioside: sequenced
Sulfatides: identified as target autoantigen

The 64,000-[M.sub.r] antigen has been completely identifiable as the lower isoform of GAD ([GAD.sub.65]). Several groups have identified ICAs to be often reactive to the [GAD.sub.65] antigen where ICA absorption can be accomplished by whole recombinant [GAD.sub.65] but not by GAD fragments, confirming reactivity to conformational epitopes. GAD antibodies also were found to react to a linear epitope; a finding that might imply a secondary autoimmunization by release of a denatured form of GAD following [beta]-cell lysis. The two isoforms of GAD have an |70% homology. However, most investigators to date have found only modest frequencies of autoantibodies to the higher molecular weight [GAD.sub.67] in IDDM patients. In other instances, ICA cannot be removed by reacting positive sera with recombinant [GAD.sub.65], indicating that other antigenic reactions are involved, especially in [ICA.sup.+] patients who are proceeding towards or have actually developed IDDM. The 38,000-[M.sub.r] antigen may be one such antigen, but its structure has yet to be identified. Glycolipids have long been recognized as an ICA antigen. Recently, a GM2-1 ganglioside has been specifically implicated as an ICA antigen. Sulfatides represent another possible candidate with high frequencies of anti-sulfatide autoantibodies reported in IDDM. Another antigen of interest is a 69,000-[M.sub.r] islet cell protein with homology to BSA, recently implicated as an environmental trigger for IDDM through molecular mimicry. Yet others include a 52,000-[M.sub.r] protein with homologies to a rubella capsid antigen, a 62,000-[M.sub.r] heat shock protein, membrane-associated proteins of 155,000 and 160,000 [M.sub.r], and a 37,000- to 40,000-[M.sub.r] glycoprotein seen in tryptic digests of islet preparations. Peripheral blood monocytes have been found to react to [GAD.sub.65], islet cell 38,000-[M.sub.r] protein, and uncharacterized antigens of 32,000, 55,000-72,000m and 120,000-170,000 [M.sub.r]. In the NOD mouse, T-cell reactivity to GAD, insulin, peripherin, heat shock protein 60, and carboxypeptidase H has been found beginning near the time of weaning.

The ability to predict impending IDDM both in relatives of affected patients as well as in general populations of school children through ICA analysis has been demonstrated by many groups. The youngest antibody positive individuals, those with higher titers, those with the IDDM-associated DQ alleles, and those with more than one IDDM-associated antibody are at greatest risk of progression to clinical disease. The greatest impediment to consistency with such studies, however, remains with the variability between laboratories in their sensitivity to measure lower titers of ICA, especially of [is less than or equal to]20 JDF U. Hopefully, future developments in the GAD autoantibody methodology will permit a more screening-reproducible test. To that end, the first workshop for GAD autoantibodies was held and revealed that the many different assays had fair specificities but limited sensitivities. Assays based on whole recombinant [GAD.sub.65], especially those using eukaryotic expression systems, should have improved sensitivities in the near future. It remains unclear at what age the pathogenic process of IDDM begins or what induces it. One study indicated that IAA could appear as early as birth when the father had IDDM, whereas others had found that coxsackie virus might be an inductive agent because its P-2C protein has homologies to GAD, GAD antibodies follow coxsackie infections, and experimental immunizations against coxsackie proteins induced anti-GAD responses. TABLE 3 Discussed

methods of preventing IDDM

Prophylactic S.Q. insulin Oral insulin/[GAD.sub.65] tolerance Insulin vaccination Intravenous [GAD.sub.65] tolerance Recombinant IL-4 Tolerogenic anti-CD4 antibodies Anti-TNF-[alpha] antibodies Tuberculin/CFA Regulatory T-cells from AMLR T-cell clones from insulitis

PATHOGENESIS AND PREVENTION

It has been shown previously that immunosuppressive drugs can be used to induce metabolic remissions in newly diagnosed patients. However, more recent studies have shown that such remissions tend not to be sustainable over time despite continuation of the therapy. An open pilot study of low dose cyclosporin in 3 of 4 high-risk [ICA.sup.+] French children showed improvement in their first-phase insulin responses to intravenous glucose. Whereas the potential for adverse side effects, especially those of viral-associated neoplasias (e.g., Epstein-Barr virus related B-cell lymphoma), inhibit widespread trials of this sort, there is increasing interest in less invasive approaches (Table 3).

The immunosuppressant mycophenolic acid is an IMP dehydrogenase inhibitor that depletes GTP, especially in activated lymphocytes, and arrests their DNA synthesis with only limited potential for neoplasia induction. When given to BB rats, the agent can both prevent diabetes and inhibit insulitis. Although it had been shown that antibody therapy prevented insulitis and diabetes when given to NOD mice to deplete them of [CD4.sup.+] T-cells, long-term protection from diabetes (? tolerance to islet cell antigens) could also be induced by nondepleting anti-CD4+ antibodies if given to young animals.

A common denominator to immunologically mediated islet cell destruction may be the damage inflicted by superoxides and nitric oxide. Both mediators inflict DNA breaks, which are repaired through the action of PARP. This repair process is accompanied by a fall in [beta]-cell NAD. Nicotinamide is an agent that can replenish intracellular NAD and, at high doses, may inhibit PARP. It can also inhibit IL-1--induced nitric oxide formation by rat islets. High doses of nicotinamide also can delay onset of diabetes in NOD mice. The long-term inhibition of PARP by high doses of nicotinamide carries the theoretical risk of neoplasia, raising concerns that such a risk needs to be considered in human trials. After preliminary findings in [IA.sup.+] relatives of patients with IDDM that administration of the vitamin may delay onset of IDDM, a large population-based study has been initiated in New Zealand school children who have screened positive for ICA. One premise of the study is that ICA in such children will predict IDDM similarly to that among relatives, and such appears to be the case in the independent Florida studies. To date, the [ICA.sup.+] New Zealand school children treated with nicotinamide do appear to have a lower than expected rate of IDDM. This rate is less than that observed in historical controls, or in that of a cohort followed in parallel that was not tested or treated. Other antioxidant inhibitors, such as probucol and its derivatives, have antidiabetic properties in rodents, but to date no human trials have been reported.

Another related approach being explored in rodents involves inhibition of the inducible form of nitric oxide synthase using aminoguanidine. [beta]-cell production of nitric oxide can be induced with IL-1 and TNF-[alpha], and potentially damaging levels of nitric oxide can be generated by macrophages within the insulitis lesions. Whereas aminoguanidine has minimal side effects, it may not be applicable to human IDDM because it remains unclear whether human macrophages can actually liberate the quantities of nitric oxide seen from rodent macrophages. Thus, nitric oxide might not have a pathogenic role in the IDDM seen in humans.

Polyinosine-polycytidine is a powerful inducer of IFN-[alpha] that when administered to BB rats can accelerate their diabetes, albeit,

opposite effects have been reported in NOD mice. A transgenic mouse expressing IFN-[alpha] in islets develops diabetes accompanied by insulitis, an outcome that is inhibitable by administration of an antibody to the cytokine. It has been reported previously that [beta]-cells of newly diagnosed IDDM patients often express IFN-[alpha], a finding that led to the hypothesis that viruses could be initiating the lesions. Taken together, these findings could argue the case for therapeutic potential for antibodies to IFA-[alpha] to prevent human IDDM.

In several laboratories, it has become clear that not all insulitis is destructive. Such was evident in murine genetic studies where insulitis could be mapped separately from diabetes, as well as after the administration of CFA to NOD mice. CFA is a lipid adjuvant containing tuberculin antigen that has been shown to induce an increase in intra-islet IL-4 producing T-cells (Th2), and a reduction in potentially damaging IFN-[gamma] T-cells (Th1 and [CD8.sup.+] cells). Thus, the concept began to emerge that [beta]-cell injury might be linked to a Th1 (IL-2, IFN-[gamma], delayed hypersensitivity) function and protection with Th2 cells (IL-4, IL-7, IL-10, TGF-[beta], antibody formation) property. However, one group reported that the insulitis lesions of the NOD were relatively devoid of T-cells expressing mRNA for IL-2, indicating an age-related predominance of Th2 cells in the infiltrate. In this regard, it was interesting that immunization of NOD mice with B-chain insulin but not A-chain insulin in IFA could powerfully prevent diabetes but not insulitis. The protection so induced could be transferred by splenocytes in cotransfer experiments. The study evoked images of future trials of vaccination by islet cell antigen fragments to prevent IDDM. Treatments of NOD mice with IL-4 could also be used to prevent diabetes. It has also been shown by two groups that oral feedings of insulin or GAD can induce a delay in the onset of diabetes in NOD mice. The effect is thought to be attributable to an active antigen-specific tolerogenesis that induces regulatory T-cells to traffic to the islet to encounter their target antigen. By so doing, they may release inhibitory cytokines such as IL-4, TGF-[beta], and/or IL-10, and inhibit local ongoing inflammatory responses through a nonantigen specific bystander effect. One study even suggested that oral feedings of glucagon may be effective, suggesting that the tolerogenic antigen needs be organ specific but not necessarily involved in the disease process.

TRANSPLANTATION BIOLOGY

There are qualitative differences between the hosts' reaction to allografts versus xenografts. In the case of the allograft response, both [CD4.sup.+] and [CD8.sup.+] T-cels are involved, but in some particular cases, [CD4.sup.+] T-cells are not required. In contrast, in xenogeneic responses, the [CD8.sup.+] T-cell plays a less prominent role. For example, the [CD8.sup.+] T-cell is not involved in the destructive process of rat islets when transplanted into mice. Thus, allogeneic graft rejection is [CD8.sup.+] T-cell--dependent, whereas that of xenogeneic graft rejection is [CD4.sup.+] T-cell--dependent. Thus, it would appear that the xenograft reaction is akin to the disease process underlying IDDM, and is the result of nonclass I MHC-restricted inflammatory tissue damage.

This shift in emphasis concerning xenogeneic reactions is important because in the past, the xeno reaction has been considered a more intense but otherwise similar form of the allograft response. It has been clear for years that immunological tolerance can be induced in animals by their treatment at the perinatal phase of development. This has been most readily demonstrated in rodents where a brief tolerogenic window after birth has been shown. However, tolerance may also be induced in adult animals as well. Tolerance can be maintained by a passive process, too, such as clonal deletion of potentially reactive T-cells or by their being rendered anergic. Tolerance can also be maintained by active mechanisms by which the

destructive function of the immune system is negatively regulated or suppressed.

This latter form of tolerance is observed when antigen is introduced into the immune system of adult animals in an appropriate form to facilitate it. When fibroblasts are made transgenic for the expression of class I MHC antigen, a suppressive form of tolerance can be induced in adult animals when the cells are grafted into them. These studies demonstrate that an active suppressive form of tolerance can be induced in adult animals and that the way the antigen is introduced can dramatically affect the outcome. That is to say, the means of antigen presentation to the immune system may determine whether an immunizing or tolerizing response results. The antigen dose, the route of injection, and the form of antigen presentation are all factors that influence the outcomes in such situations. The fact that tolerance can be induced even in adult animals offers much hope for the treatment of diabetes by islet grafting in the future, but much more work is needed to elucidate the mechanisms responsible for the maintenance of tolerance once induced.

The relative roles of macrophages versus dendritic cells in antigen presentation in inflammatory responses versus graft rejection mechanisms appear to be important. It was shown that pig islets could function in NOD mice long term, provided that the mice were treated with anti-CD3 and CD4 antibodies and the grafts were exposed to high concentrations of oxygen before their transplantation. When the outcome was successful, the native islets were still often infiltrated, whereas the xenografts appeared to be relatively resistant to autoimmune attack. In BBZ/Wor rats, diabetes appeared to result from reduced [beta]-cell mass from the autoimmune process as well as reduced [beta]-cell responsiveness to glucose as a result of GLUT2 loss. It is not known whether the finding would extend to other models or to islet cell transplant situations. IL-1 has been shown to induce an inducible form of nitric oxide synthase within islet cells, raising the possibility that toxic levels of nitric oxide may arise within these cells when undergoing islet rejection or autoimmune attack. Mice expressing the EBV receptor CR2 in their [beta]-cells were found to develop a peri-islet infiltrate but not an intra-islet inflammation or diabetes, suggesting that another signal event might be required for this to occur.

Progress continues in allogeneic and xenogeneic islet transplantation using hybrid pancreatic devises in diabetic rats and dogs. Such transplantations exclude the immune system from direct attack and have functioned for as long as a year. One group reported long-term success with pig islets in a single coiled acrylic copolymer capillary implant in ALX-treated rabbits. Of the studies reported, the predominant long-term hope for the restitution of islet cell function in patients with longstanding IDDM may lie with xenogenic grafts.

SUMMARY

The number and complexity of genetic susceptibilities in the NOD mouse and patients with IDDM is growing rapidly, with a dichotomy seen in respect to the predispositions to insulitis and/or diabetes. Insulitis in many circumstances was seen to be protective, a type of response that appeared to increase relatively with age in the NOD mouse and could be induced by several means, such as treatment with BCG/CFA; by perturbations of the phenotype of invading cells, especially in respect to their expressed cytokines; through orally induced tolerance to islet antigens; or even by tolerogenesis induced by active immunization to islet antigens in IFA. Much progress has been made in respect to the identification of islet cell antigen targeted by the autoimmune response, and their relative pathogenic roles need examination. Various assays for GAD have appeared and hold promise of improved methods of screening persons susceptible to IDDM. The 38,000-[M.sub.r] antigen, however, still needs elucidation. Many

potential treatments to prevent IDDM have appeared, and human trials have begun. Progress in islet cell transplantation continues to be made, but functional xenogeneic grafts in diabetic humans still appear distant. We look forward to further progress to be reported at the 13th meeting scheduled to take place in Paris, France, in June 1994.

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SPECIAL FEATURES: illustration; table
DESCRIPTORS: Diabetes--Research; Diabetes, Insulin-dependent--Genetic aspects; Transplantation of organs, tissues, etc.--Research
FILE SEGMENT: HI File 149

14/9/7 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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15123610 Genuine Article#: VL103 Number of References: 23
Title: GENETIC SUSCEPTIBILITY TO EXPERIMENTAL AUTOIMMUNE UVEORETINITIS IN THE RAT IS ASSOCIATED WITH AN ELEVATED TH1 - RESPONSE
Author(s): CASPI RR; SILVER PB; CHAN CC; SUN B; AGARWAL RK; WELLS J; ODDO S ; FUJINO Y; NAJAFIAN F; WILDER RL
Corporate Source: NEI,IMMUNOL LAB,NIH,BLDG 10,ROOM 10N222,10 CTR DR,MSC 1858/BETHESDA//MD/20892; NIAMSD,NATL INST HLTH/BETHESDA//MD/20892
Journal: JOURNAL OF IMMUNOLOGY, 1996, V157, N6 (SEP 15), P2668-2675
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Geographic Location: USA
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: IMMUNOLOGY
Abstract: This study examines whether genetic susceptibility vs genetic resistance to experimental autoimmune uveoretinitis (EAU) are connected to a predisposition to mount a Th1-dominated (IFN-gamma high, IL-4 low) vs a Th2-dominated (IL-4 high, IFN-gamma low) response, Lewis rats developed disease with high incidence after immunization with the uveitogenic peptide R16, whereas F344 rats were resistant. Primed lymph node cells from both strains proliferated in culture in response to R16, However, while the Lewis cultures transferred EAU to syngeneic recipients, those of F344 did not, The Lewis cultures produced substantially more IFN-gamma mRNA and protein in response to R16, than did those of F344, Both strains made low levels of IL-10 mRNA and IL-4 mRNA. Unlike the primary cultures, long-term (R16-specific) T cell lines derived from each of the strains transferred EAU equally well to their respective recipients, and produced similar, high levels of IFN-gamma mRNA and protein, Treatment of F344 with Bordefella pertussis toxin concurrently with immunization abrogated its resistance,enhanced Ag-specific IFN-gamma production in culture, and yielded a primed cell population capable of transferring EAU, Conversely, immunization of Lewis rats with R16 in IFA induced little or no disease; the primed cells produced minimal amounts of IFN-gamma and did not transfer EAU. However, addition of IL-12 into the culture resulted in a highly pathogenic, IFN-gamma-producing cell population, We conclude that genetic susceptibility to ocular autoimmunity in this model is connected to an elevated Th1 response, Genetic resistance, however, does not seem to involve an elevated Th2 response, but rather an inhibited development of Th1-like effector cells.
Identifiers--KeyWords Plus: T-CELLS; MHC
Research Fronts: 94-5856 001 (EXPERIMENTAL AUTOIMMUNE UVEITIS; LEWIS

RATS; BILATERAL RETINAL RESPONSES DURING THE ACUTE-PHASE (4-14-DAYS))
Cited References:

CASPI RR, 1994, P55, ADV OCULAR IMMUNOLOG
CASPI RR, 1994, AUTOIMMUNE DIS MODEL
CASPI RR, 1992, V11, P81, CURR EYE RES
CASPI RR, 1986, V136, P928, J IMMUNOL
CASPI RR, 1992, V148, P2384, J IMMUNOL
CASPI RR, 1994, V152, P890, J IMMUNOL
CASPI RR, 1993, V4, P321, REG IMMUNOL
CHOMCZYNSKI P, 1993, V15, P532, BIOTECHNIQUES
CUA KJ, 1995, V155, J IMMUNOL
FERBER IA, 1996, V156, P5, J IMMUNOL
GERY I, 1986, V5, P75, PROGR RETINAL RES
KOTEWICZ ML, 1988, V16, P265, NUCLEIC ACIDS RES
LIBLAU RS, 1995, V16, P34, IMMUNOL TODAY
NUSSENBLATT RB, 1996, P22, UVEITIS FUNDAMENTALS
ROOK GAW, 1994, V15, P301, IMMUNOL TODAY
SANUI H, 1989, V169, P1947, J EXP MED
SAOUDI A, 1993, V23, P3096, EUR J IMMUNOL
SAOUDI A, 1995, V182, P335, J EXP MED
SAVION S, 1994, V55, P35, J NEUROIMMUNOL
SCOTT B, 1994, V1, P73, IMMUNITY
SNEDECOR GW, 1967, P248, STATISTICAL METHODS
STEWART WE, 1979, P17, INTERFERON SYSTEM
SUN B, 1996, IN PRESS J IMMUNOL M

14/9/8 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci

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15033202 Genuine Article#: VE109 Number of References: 28
Title: IL-12 PROMOTES CELLULAR BUT NOT HUMORAL TYPE-II COLLAGEN-SPECIFIC T(H)1-TYPE RESPONSES IN C57BL/6 AND B10.Q MICE AND FAILS TO INDUCE ARTHRITIS

Author(s): SZELIGA J; HESS H; RUDE E; SCHMITT E; GERMANN T
Corporate Source: INST IMMUNOL,OBERE ZAHLBACHER STR 67/D-55101 MAINZ//GERMANY/; INST IMMUNOL/D-55101 MAINZ//GERMANY/

Journal: INTERNATIONAL IMMUNOLOGY, 1996, V8, N8 (AUG), P1221-1227
ISSN: 0953-8178
Language: ENGLISH Document Type: ARTICLE
Geographic Location: GERMANY
Subfile: SciSearch; CC LIFE--Current Contents, Life Sciences
Journal Subject Category: IMMUNOLOGY

Abstract: DBA/1 (H-2(q)) and C57BL/6 (H-2(b)) mice develop an intermediate immune response when immunized with chicken type II collagen (CII) emulsified with incomplete Freund's adjuvant (IFA), Only a few animals develop a mild form of arthritis, As reported before and confirmed herein, administration of IL-12 to DBA/1 mice immunized with CII in IFA strongly enhances the cellular and humoral (auto)immune response to CII and induces severe destructive joint disease with an incidence of 80-100%, In contrast, the same treatment did not promote joint disease in C57BL/6 mice, Characterization of the IL-12 effect on the CII-specific immune response of C57BL/6 mice revealed that IL-12 promoted the development of CII-specific T cells producing IFN-gamma in DBA/1 and C57BL/6 mice equally well, However, whereas treatment with IL-12 in DBA/1 mice strongly up-regulated the synthesis of CII-specific antibodies, especially of the IgG2a and IgG2b subclasses, it rather

slightly down-regulated the CII-specific IgG2a and IgG2b synthesis in C57BL/6 mice, This may indicate that the effect of IL-12 on the CII-specific antibody synthesis is of crucial importance in the pathogenesis of type II collagen-induced arthritis (CIA), The failure of IL-12 to up-regulate IgG2a and IgG2b synthesis in C57BL/6 mice is specific for CII as antigen and not a general property of this strain because the keyhole limpet hemacyanin-specific antibody response is up-regulated by IL-12 in C57BL/6 mice, Furthermore, it is not the H-2(b) haplotype of C57BL/6 mice but rather the genetic background (DBA/1 versus BL/6 or BL/10) that limits the effect of IL-12 on the CII-specific antibody response because IL-12 treatment of CII-immunized B10.Q (H-2(q)) mice also failed to induce arthritis and to enhance CII-specific IgG2a and IgG2b synthesis, However, as in the two other strains, injection of IL-12 promoted the development of splenic T cells producing IFN-gamma upon activation with CII, These results indicate that an enhancement of the cellular and humoral anti-Cll response by IL-12 is required for inducing arthritis.

Descriptors--Author Keywords: ANTIBODY RESPONSE ; AUTOIMMUNITY ; GENETIC BACKGROUND

Identifiers--KeyWords Plus: INDUCED MURINE ARTHRITIS; IN-VIVO; MEDIATED-IMMUNITY; T-CELLS; INTERLEUKIN-12; SUSCEPTIBILITY; ANTIBODY; LYMPHOCYTES; CYTOKINE; EXPRESSION

Research Fronts: 94-1498 003 (CYTOKINES IN LEISHMANIASIS; TH2 CELLS; IMMUNOLOGICAL ASPECTS OF ASTHMA; HUMAN ALLERGIC RESPONSE)

Cited References:

BOTTOMLY K, 1988, V9, P268, IMMUNOL TODAY
BRUNSBERG U, 1994, V24, P1698, EUR J IMMUNOL
DANDREA A, 1992, V176, P1387, J EXP MED
FISCHER S, 1993, V189, P40, IMMUNOBIOLOGY
GATELY MK, 1994, V6, P157, INT IMMUNOL
GERMANN T, 1995, V25, P823, EUR J IMMUNOL
GERMANN T, 1995, V92, P4823, P NATL ACAD SCI USA
HOLMDAHL R, 1988, V65, P305, IMMUNOLOGY
HSIEH CS, 1993, V260, P547, SCIENCE
JANICKI BW, 1970, V105, P527, J IMMUNOL
JANSSON L, 1993, V94, P459, CLIN EXP IMMUNOL
JELINEK DF, 1995, V154, P1606, J IMMUNOL
KINIWA M, 1992, V90, P262, J CLIN INVEST
MCKNIGHT AJ, 1994, V152, P2172, J IMMUNOL
MORRIS SC, 1994, V152, P1047, J IMMUNOL
PARISH CR, 1971, V134, P21, J EXP MED
RIZZO LV, 1995, V25, P708, EUR J IMMUNOL
SCHMITT E, 1994, V24, P343, EUR J IMMUNOL
SCOTT P, 1993, V260, P496, SCIENCE
SEKI N, 1988, V140, P1477, J IMMUNOL
SEKI N, 1992, V148, P3093, J IMMUNOL
TAYLOR PC, 1995, V25, P763, EUR J IMMUNOL
TITE JP, 1987, V139, P2892, J IMMUNOL
TREMBLEAU S, 1995, V16, P383, IMMUNOL TODAY
TRENTHAM DE, 1982, V25, P911, ARTHRITIS RHEUM
TRINCHIERI G, 1994, V84, P4008, BLOOD
WATSON WC, 1985, V162, P1878, J EXP MED
WOOLEY PH, 1981, V154, P688, J EXP MED

14/9/9 (Item 1 from file: 636)
DIALOG(R)File 636:IAC Newsletter DB(TM)
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03259419
Autoimmune Encephalomyelitis: Birnbaum, G.; Kotilinek, L.; Schlievert, P.; Clark, H.B.; Trotter, J.; Horvath, E.; Gao, E.; Cox, M.; Braun, P.E.
"Heat Shock Proteins and Experimental Autoimmune Encephalomyelitis (EAE) .1. Immunization with a Peptide of the Myelin Protein 2',3' Cyclic Nucleotide 3' Phosphodiesterase That Is Cross-Reactive with a Heat Shock Protein Alters the Course of EAE."
Vaccine Weekly July 8, 1996
ISSN: 1074-2921 WORD COUNT: 327
PUBLISHER: Charles W Henderson

Journal of Neuroscience Research, May 15, 1996;44(4):381-396.

According to the authors' abstract of an article published in Journal of Neuroscience Research, "We describe sequence similarity and immunologic cross-reactivity between a peptide of the mycobacterial hsp, HSP65, and the myelin protein 2',3' cyclic nucleotide 3' phosphodiesterase (CNP). We demonstrate that immunization with the homologous crossreactive CNP peptide (hsp-CNP peptide) has significant biological consequences. Rats immunized with hsp-CNP peptide in either complete Freund's adjuvant (CFA) or incomplete Freund's adjuvant (IPA) produce large amounts of peptide-specific antibody. Isotypes of antibodies in animals immunized with peptide in CFA are IgG1 and IgG2a. Isotypes of antibodies in rats immunized with peptide in IFA are predominantly IgG1, with low titers of IgG2a. T-cell proliferative responses to HSP65 are present in rats immunized with peptide in CPA. T-cell responses to HSP65 initially are absent in rats immunized with peptide in IFA but develop over time. T-cell proliferative responses to hsp-CNP peptide were not detected. None of the groups of rats developed clinical or histologic evidence of experimental autoimmune encephalomyelitis (EAE). To induce EAE, rats preimmunized with hsp-CNP peptide were challenged with guinea pig spinal cord (GPSC) emulsified in CFA. Rats preimmunized with peptide in CFA developed severe EAE. Rats preimmunized with hsp-CNP peptide in IFA were protected from EAE, with both a lower incidence and severity of disease. Injecting the murine monoclonal antibody recognizing the shared HSP65 and CNP epitope did not protect against EAE. Our data suggest that a Th2 pattern of immune response to a CNP peptide that itself is non-encephalitogenic protects against EAE. Immune responses to either hsp or myelin proteins cross-reactive with hsp may play an important role in the development of EAE." The corresponding author for this study is: G Birnbaum, Univ Minnesota Hosp & Clin, Dept Neurol, Box 295, Minneapolis, MN 55455 USA. For subscription information for this journal contact the publisher: Wiley-Liss, Div John Wiley & Sons Inc, 605 Third Ave, New York, NY 10158-0012.
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INDUSTRY: Medical and Health (MH)
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S3         129   E1-E14
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S5          15   S4 AND TH2
S6           8   RD (unique items)
S7          23   TH2 AND AUTOIMMUN
S8        1403   TH2 AND AUTOIMMUN?
S9         120   S8 AND ADJUVANT?
S10        120   S9
S11         78   RD (unique items)
S12         78   S11 NOT S6
S13         16   S8 AND IFA
S14          9   RD (unique items)
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Processing
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             84656   MYELIN
            741220   BASIC
           4168824   PROTEIN
             24443   MYELIN(W)BASIC(W)PROTEIN
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```
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Production of tumor necrosis factor-alpha as a result of glia-T-cell interaction correlates with the pathogenic activity of myelin basic protein-reactive T cells in experimental autoimmune encephalomyelitis
Sun D; Hu X; Shah R; Zhang L; Coleclough C
Dep. Immunol., St. Jude Children's Res. Hosp., PO Box 318, Memphis, TN 38105, USA
Journal of Neuroscience Research 45 (4). 1996. 400-409.
Full Journal Title: Journal of Neuroscience Research
ISSN: 0360-4012
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Neonatal or adult injection of MBP in IFA induces a vigorous TH2-type T cell response
Forsthuber T; Cheng H; Karulin A; Lehman P
Case Western Reserve Univ., Sch. Med., Dep. Pathol., Cleveland, OH 44106, USA
Journal of Neuroimmunology 0 (SUPPL. 1). 1995. 66.
Full Journal Title: 11th European Congress on Multiple Sclerosis. Journal of Neuroimmunology
ISSN: 0165-5728
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 003 Ref. 040364

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Protracted, relapsing and demyelinating experimental autoimmune encephalomyelitis in DA rats immunized with syngeneic spinal cord and incomplete Freund's adjuvant
Lorentzen J C; Issazadeh S; Storch M; Mustafa M I; Lassman H; Linington C ; Klareskog L; Olsson T
Dep. Rheumatol., Karolinska Hospital, Karolinska Inst., S-17176 Stockholm, Sweden
Journal of Neuroimmunology 63 (2). 1995. 193-205.
Full Journal Title: Journal of Neuroimmunology
ISSN: 0165-5728
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 005 Ref. 068121

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Self and non-self peptides treat autoimmune encephalomyelitis: T cell

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Gautam A M
Human Genetics Group, John Curtin Sch. Med. Res., Australian Natl. Univ., Canberra, ACT 2601, Australia
European Journal of Immunology 25 (7). 1995. 2059-2063.
Full Journal Title: European Journal of Immunology
ISSN: 0014-2980
Language: ENGLISH
Print Number: Biological Abstracts Vol. 100 Iss. 005 Ref. 068925

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STUDIES OF V-BETA-8 T CELL RECEPTOR PEPTIDE TREATMENT IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS
STEVENS D B; KARPUS W J; GOULD K E; SWANBORG R H
DEP. IMMUNOLOGY MICROBIOLOGY, WAYNE STATE UNIV. SCH. MED., 540 EAST CANFIELD AVENUE, DETROIT, MICH. 48201, USA.
J NEUROIMMUNOL 37 (1-2). 1992. 123-129. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH

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ABROGATION OF INDUCED RESISTANCE TO EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN GUINEA-PIGS BY HOST-VERSUS-GRAFT REACTION
KOZOVSKA M; STAYKOVA M; GORANOV I
INST. CELL BIOL. MORPHOL., ACAD. G. BONTCHEV STR. 25 1113 SOFIA, BULGARIA.
J NEUROIMMUNOL 29 (1-3). 1990. 157-164. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH

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GENERATION OF CD4-POSITIVE T CELLS IN RECIPIENTS OF BP-IFA-SENSITIZED SPLEEN CELLS
KIRA J-I; ITOYAMA Y; GOTO I
DEP. NEUROL., NEUROL. INST., FAC. MED., KYUSHU UNIV., FUKUOKA 812, JPN.
CELL IMMUNOL 128 (1). 1990. 130-141. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH

16/3/8 (Item 8 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

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7353487 BIOSIS Number: 89004506
GENERATION OF CD4-POSITIVE BLASTOID T CELLS SHOWING MARKED UPREGULATION OF CD4 CLASS I AND II MHC AND IL2 RECEPTOR MOLECULES IS REQUIRED FOR THE EXPRESSION OF POTENT ENCEPHALITOGENICITY
KIRA J-I; ITOYAMA Y; GOTO I
DEP. NEUROL., NEUROLOGICAL INST., FAC. MED., KYUSHU UNIV., FUKUOKA 812, JAPAN.
CELL IMMUNOL 123 (2). 1989. 264-275. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH

16/3/9 (Item 9 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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THE ROLE OF MYELIN LIPIDS IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS III. TRANSFER OF SUPPRESSION FROM GUINEA-PIGS RECOVERING FROM EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS INDUCED BY MYELIN BASIC PROTEIN-GALACTOCEREBROSIDE COMPLEXES
HOSEIN Z Z; GILBERT J J; STREJAN G H
DEP. OF IMMUNOL, KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN.
CELL IMMUNOL 99 (1). 1986. 265-278. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH

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4816532 BIOSIS Number: 79058847
SUPPRESSION OF CHRONIC-RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN STRAIN-13 GUINEA-PIGS BY ADMINISTRATION OF LIPOSOME-ASSOCIATED MYELIN BASIC PROTEIN
STREJAN G H; GILBERT J J; ST LOUIS J
DEP. MICROBIOLOGY IMMUNOLOGY, UNIV. WESTERN ONT., HEALTH SCI. CENTER, LONDON, ONT., CAN.
J NEUROIMMUNOL 7 (1). 1984. 27-42. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH

16/3/11 (Item 11 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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4502048 BIOSIS Number: 78075871
PARTICIPATION OF ENCEPHALITOGEN IN INCOMPLETE FREUNDS ADJUVANT IN THE INDUCTION OF EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN HARTLEY GUINEA-PIGS
LEBAR R; VINCENT C
U 23 INSERM, HOPITAL ST-ANTOINE, 184, RUE DE FG ST-ANTOINE, 75571 PARIS CEDEX 12, FR.
J NEUROIMMUNOL 6 (3). 1984. 187-196. CODEN: JNRID

Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH

16/3/12 (Item 12 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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4352432 BIOSIS Number: 77027759
ACUTE EXPERIMENTAL AUTO IMMUNE ENCEPHALO MYELITIS DIFFERENCES BETWEEN T CELL SUBSETS IN THE BLOOD AND MENINGEAL INFILTRATES IN SUSCEPTIBLE AND RESISTANT STRAINS OF GUINEA-PIGS
TRAUGOTT U
DEP. PATHOL., K-433, ALBERT EINSTEIN COLL. MED., 1300 MORRIS PARK AVE., BRONX, N.Y. 14061, USA.
J NEUROL SCI 61 (1). 1983. 81-92. CODEN: JNSCA
Full Journal Title: Journal of the Neurological Sciences
Language: ENGLISH

16/3/13 (Item 13 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3988361 BIOSIS Number: 75035720
CHRONIC RELAPSING EXPERIMENTAL AUTO IMMUNE ENCEPHALO MYELITIS TREATMENT WITH COMBINATION OF MYELIN COMPONENTS PROMOTES CLINICAL AND STRUCTURAL RECOVERY
TRAUGOTT U; STONE S H; RAINE C S
DEPARTMENT OF PATHOLOGY, K-433, ALBERT EINSTEIN COLLEGE OF MEDICINE, 1300 MORRIS PARK AVENUE, BRONX, N. Y. 10461, U.S.A.
J NEUROL SCI 56 (1). 1982. 65-74. CODEN: JNSCA
Full Journal Title: Journal of the Neurological Sciences
Language: ENGLISH

16/3/14 (Item 14 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3979119 BIOSIS Number: 75026478
AUTO IMMUNE EFFECTOR CELLS 3. ROLE OF ADJUVANT AND ACCESSORY CELLS IN THE IN-VITRO INDUCTION OF AUTO IMMUNE ENCEPHALO MYELITIS
KILLEN J A; SWANBORG R H
DEP. IMMUNOL. MICROBIOL., WAYNE STATE UNIV. SCH. MED., DETROIT, MICH. DETROIT 48201.
J IMMUNOL 129 (2). 1982. 759-763. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

16/3/15 (Item 15 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3768899 BIOSIS Number: 74068762
CHRONIC RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IDENTIFICATION AND DYNAMICS OF T AND B CELLS WITHIN THE CENTRAL NERVOUS SYSTEM

TRAUGOTT U; SHEVACH E; CHIBA J; STONE S H; RAINE C S
DEP. PATHOL., ALBERT EINSTEIN COLL. MED., BRONX, NY 10461.
CELL IMMUNOL 68 (2). 1982. 261-275. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH

16/3/16 (Item 16 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3724878 BIOSIS Number: 74024741
TRANSFER OF ALLERGIC ENCEPHALO MYELITIS WITH SPLEEN CELLS FROM DONORS SENSITIZED WITH MYELIN BASIC PROTEIN IN INCOMPLETE FREUNDS ADJUVANT
NAMIKAWA T; RICHERT J R; DRISCOLL B F; KIES M W; ALVORD E C JR
SECT. MYELIN CHEM., LAB. CEREBRAL METAB., NATL. INST. MENT. HEALTH, BETHESDA, MD. 20205.
J IMMUNOL 128 (2). 1982. 932-934. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

16/3/17 (Item 17 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3655931 BIOSIS Number: 73048298
INDUCTION OF LETHAL EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN NONHUMAN PRIMATES AND GUINEA-PIGS WITH HUMAN GLIO BLASTOMA MULTIFORME TISSUE
BIGNER D D; PITTS O M; WIKSTRAND C J
DEP. PATHOL., DUKE UNIV. MED. CENT., DURHAM, N.C. 27710.
J NEUROSURG 55 (1). 1981. 32-42. CODEN: JONSA
Full Journal Title: Journal of Neurosurgery
Language: ENGLISH

16/3/18 (Item 18 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3654567 BIOSIS Number: 73046934
SUPPRESSION OF EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN GUINEA-PIGS BY LIPOSOME ASSOCIATED HUMAN MYELIN BASIC PROTEIN
STREJAN G H; PERCY D H; ST LOUIS J; SURLAN D; PATY D W
DEP. OF MICROBIOL. AND IMMUNOL., UNIV. OF WESTERN ONTARIO, LONDON, ONTARIO, CANADA.
J IMMUNOL 127 (5). 1981. 2064-2069. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

16/3/19 (Item 19 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1996 BIOSIS. All rts. reserv.

3114973 BIOSIS Number: 70064880
IN-VITRO RESPONSE TO BASIC PROTEIN IN EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS EFFECT OF PRE TREATMENT WITH BASIC PROTEIN IN INCOMPLETE ADJUVANT

LISAK R P; ZWEIMAN B; DZIDA L; ROSENBLUM F; RORKE L B; BARGER G
DEP. NEUROL., DIV. ALLERGY IMMUNOL., DEP. MED., SCH. MED., UNIV. PA., PHILADELPHIA, PA. 19104, USA.
CELL IMMUNOL 52 (2). 1980. 443-450. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH

16/3/20 (Item 20 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3080665 BIOSIS Number: 70030572
FAILURE OF MYELIN BASIC PROTEIN TO PREVENT OR SUPPRESS EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN GUINEA-PIGS
HASHIM G A
DEP. SURG., ST. LUKE'S HOSP. CENT., NEW YORK, N.Y. 10025, USA.
NEUROCHEM RES 5 (2). 1980. 101-114. CODEN: NERED
Full Journal Title: Neurochemical Research
Language: ENGLISH

16/3/21 (Item 21 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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2723400 BIOSIS Number: 67060803
REGULATION OF SELF TOLERANCE IN EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS PART 1 DIFFERENCES BETWEEN LYMPH NODE AND SPLEEN SUPPRESSOR CELLS
WELCH A M; SWIERKOSZ J E; SWANBORG R H
DEP. IMMUNOL. MICROBIOL., WAYNE STATE UNIV. SCH. MED., DETROIT, MICH. 48201, USA.
J IMMUNOL 121 (5). 1978. 1701-1705. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

16/3/22 (Item 22 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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2407367 BIOSIS Number: 65033775
EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN INBRED GUINEA-PIGS CORRELATION OF DECREASE IN EARLY THYMUS DERIVED CELLS WITH CLINICAL SIGNS IN SUPPRESSED AND UNSUPPRESSED ANIMALS
TRAUGOTT U; RAINE C S
DEP. PATHOL., ROSE F. KENNEDY CENT. RES. MENT. RETARD. HUM. DEV., ALBERT EINSTEIN COLL. MED., BRONX, N.Y. 10461, USA.
CELL IMMUNOL 34 (1). 1977 146-155. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH

16/3/23 (Item 23 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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2394584 BIOSIS Number: 65020992

IMMUNO REGULATION OF EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS CONDITIONS FOR INDUCTION OF SUPPRESSOR CELLS AND ANALYSIS OF MECHANISM
SWIERKOSZ J E; SWANBORG R H
DEP. MICROBIOL., UNIV. ROCHESTER SCH. MED. AND DENT., ROCHESTER, N.Y. 14620, USA.
J IMMUNOL 119 (4). 1977 1501-1506. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

16/3/24 (Item 24 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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2227533 BIOSIS Number: 64054453
SUPPRESSION OF ACUTE AND CHRONIC EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN STRAIN 13 GUINEA-PIGS A CLINICAL AND PATHOLOGICAL STUDY
RAINE C S; SNYDER D H; STONE S H; BORNSTEIN M B
J NEUROL SCI 31 (3). 1977 355-367. CODEN: JNSCA
Full Journal Title: Journal of the Neurological Sciences

16/3/25 (Item 25 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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1953676 BIOSIS Number: 62043236
PROTECTION AGAINST EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS WITH PEPTIDES DERIVED FROM MYELIN BASIC PROTEIN PRESENCE OF INTACT ENCEPHALITOGENIC SITE IS ESSENTIAL
DRISCOLL B F; KIES M W; ALVORD E C JR
J IMMUNOL 117 (1). 1976 110-114. CODEN: JOIMA
Full Journal Title: Journal of Immunology

16/3/26 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

8400792 EMBASE No: 92077516
Studies of Vbeta8 T cell receptor peptide treatment in experimental autoimmune encephalomyelitis
Stevens D.B.; Karpus W.J.; Gould K.E.; Swanborg R.H.
Department of Immunology and Microbiology, Wayne State University School of Medicine, 540 East Canfield Avenue, Detroit, MI 48201 USA
J. NEUROIMMUNOL. (Netherlands) , 1992, 37/1-2 (123-129) CODEN: JNRID
ISSN: 0165-5728
LANGUAGES: English SUMMARY LANGUAGES: English

16/3/27 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

7796472 EMBASE No: 90231421
Generation of CD4+ blastoid T cells in recipients of BP/IFA-sensitized spleen cells
Kira J.-I.; Itoyama Y.; Goto I.

Department of Neurology, Neurological Institute, Faculty of Medicine, Kyushu University, Fukuoka 812 Japan
CELL. IMMUNOL. (USA), 1990, 128/1 (130-141) CODEN: CLIMB ISSN: 0008-8749
LANGUAGES: English

16/3/28 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

6146098 EMBASE No: 86141158
The role of myelin lipids in experimental allergic encephalomyelitis. III. Transfer of suppression from guinea pigs recovering from EAE, induced by myelin basic protein-galactocerebroside complexes
Hosein Z.Z.; Gilbert J.J.; Strejan G.H.
Department of Microbiology, University of Western Ontario, London, Ont. CANADA
CELL. IMMUNOL. (USA), 1986, 99/1 (265-278) CODEN: CLIMB
LANGUAGES: ENGLISH

16/3/29 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

5630763 EMBASE No: 84126429
Participation of encephalitogen in incomplete Freund's adjuvant in the induction of experimental allergic encephalomyelitis in Hartley guinea pigs
Lebar R.; Vincent C.
Centre d'Immuno-Pathologie et d'Immunologie Experimentale, INSERM (U 23), CNRS (LA 289), Hopital St.-Antoine, 75012 Paris FRANCE
J. NEUROIMMUNOL. (NETHERLANDS), 1984, 6/3 (187-196) CODEN: JNRID
LANGUAGES: ENGLISH

16/3/30 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

5479801 EMBASE No: 83231624
Acute experimental autoimmune encephalomyelitis. Differences between T cell subsets in the blood and meningeal infiltrates in susceptible and resistant strains of guinea pigs
Traugott U.
Dep. Pathol., Albert Einstein Coll. Med., Bronx, NY 10461 USA
J. NEUROL. SCI. (NETHERLANDS), 1983, 61/1 (81-91) CODEN: JNSCA
LANGUAGES: ENGLISH

16/3/31 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

5215387 EMBASE No: 82220915
Chronic relapsing experimental autoimmune encephalomyelitis. Treatment with combinations of myeline components promotes clinical and structural recovery

Traugott U.; Stone S.H.; Raine C.S.
Dep. Pathol., Rose F. Kennedy Cent. Res. Ment. Retard. Hum. Dev., Albert Einstein Coll. Med., The Bronx, NY 10461 USA
J. NEUROL. SCI. (NETHERLANDS) , 1982, 56/1 (65-73) CODEN: JNSCA
LANGUAGES: ENGLISH

16/3/32 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

5181937 EMBASE No: 82187292
Autoimmune effector cells. III. Role of adjuvant and accessory cells in the in vitro induction of autoimmune encephalomyelitis
Killen J.A.; Swanborg R.H.
Dept. Immunol. Microbiol., Wayne State Univ. Sch. Med., Detroit, MI 48201 USA
J. IMMUNOL. (USA) , 1982, 129/2 (759-763) CODEN: JOIMA
LANGUAGES: ENGLISH

16/3/33 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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5144719 EMBASE No: 82149809
Chronic relapsing experimental allergic encephalomyelitis: Identification and dynamics of T and B cells within the central nervous system
Traugott U.; Shevach E.; Chiba J.; et al.
Dep. Pathol., Albert Einstein Coll. Med., Bronx, NY 10461 USA
CELL. IMMUNOL. (USA) , 1982, 68/2 (261-275) CODEN: CLIMB
LANGUAGES: ENGLISH

16/3/34 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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5066303 EMBASE No: 82068418
Transfer of allergic encephalomyelitis with spleen cells from donors sensitized with myelin basic protein in incomplete Freund's adjuvant
Namikawa T.; Richert J.R.; Driscoll B.F.; et al.
Sect. Myelin Chem., Lab. Cerebr. Metab., Nat. Inst. Ment. Hlth, Bethesda, MD 20205 USA
J. IMMUNOL. (USA) , 1982, 128/2 (932-934) CODEN: JOIMA
LANGUAGES: ENGLISH

16/3/35 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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2588922 EMBASE No: 81247197
Suppression of experimental allergic encephalomyelitis in guinea/pigs by liposome-associated human myelin basic protein
Strejan G.H.; Percy D.H.; St. Louis J.; et al.
Dept. Microbiol. Immunol., Univ. West. Ontario, London, Ontario CANADA
J. IMMUNOL. (USA) , 1981, 127/5 (2064-2069) CODEN: JOIMA

LANGUAGES: ENGLISH

16/3/36 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
(c) 1997 Elsevier Science B.V. All rts. reserv.

2501382 EMBASE No: 81157678
Induction of lethal experimental allergic encephalomyelitis in nonhuman primates and guinea pigs with human glioblastoma multiforme tissue
Bigner D.D.; Pitts O.M.; Wikstrand C.J.
Dept. Pathol., Duke Univ. Med. Cent., Durham, N.C. 27710 USA
J. NEUROSURG. (USA) , 1981, 55/1 (32-42) CODEN: JONSA
LANGUAGES: ENGLISH

16/3/37 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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2037184 EMBASE No: 80174129
In vitro response to basic protein in experimental allergic encephalomyelitis: Effect of pretreatment with basic protein in incomplete adjuvant
Lisak R.P.; Zweiman B.; Dzida L.; et al.
Dept. Neurol., Sch. Med., Univ. Pennsylvania, Philadelphia, Pa. 19104 USA
CELL. IMMUNOL. (USA) , 1980, 52/2 (443-450) CODEN: CLIMB
LANGUAGES: ENGLISH

16/3/38 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE
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1596694 EMBASE No: 80098072
Failure of myelin basic protein to prevent or suppress experimental allergic encephalomyelitis in guinea pigs
Hashim G.A.
Dept. Surg. Microbiol., St Luke's Hosp. Cent., New York, N.Y. 10025 USA
NEUROCHEM. RES. (USA) , 1980, 5/2 (101-113) CODEN: NERED
LANGUAGES: ENGLISH

16/3/39 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE
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1315170 EMBASE No: 79083484
Chronic relapsing experimental allergic encephalomyelitis. Correlation of circulating lymphocyte fluctuations with disease activity in suppressed and unsuppressed animals
Traugott U.; Stone S.H.; Raine C.S.
Dept. Pathol., Albert Einstein Coll. Med., Bronx, N.Y. 10461 USA
J. NEUROL. SCI. (NETHERLANDS) , 1979, 41/1 (17-29) CODEN: JNSCA
LANGUAGES: ENGLISH

16/3/40 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE
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1282570 EMBASE No: 79050429
Regulation of self tolerance in experimental allergic encephalomyelitis. I. Differences between lymph node and spleen suppressor cells
Welch A.M.; Swierkosz J.E.; Swanborg R.H.
Dept. Immunol. Microbiol., Wayne State Univ. Sch. Med., Detroit, Mich. 48201 USA
J. IMMUNOL. (USA) , 1978, 121/5 (1701-1705) CODEN: JOIMA
LANGUAGES: ENGLISH

16/3/41 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE
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1045864 EMBASE No: 78217557
Experimental allergic encephalomyelitis in inbred guinea pigs: correlation of decrease in early T cells with clinical signs in suppressed and unsuppressed animals
Traugott U.; Raine C.S.
Dept. Pathol., Rose F. Kennedy Cent. Res. Ment. Retardat. Hum. Developm., Albert Einstein Coll. Med., Bronx, N.Y. 10461 USA
CELL. IMMUNOL. (USA) , 1977, 34/1 (146-155) CODEN: CLIMB
LANGUAGES: ENGLISH

16/3/42 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE
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1044413 EMBASE No: 78216072
Immunoregulation of experimental allergic encephalomyelitis: conditions for induction of suppressor cells and analysis of mechanism
Swierkosz J.E.; Swanborg R.H.
Dept. Immunol. Microbiol., Wayne State Univ. Sch. Med., Detroit, Mich. 48201 USA
J. IMMUNOL. (USA) , 1977, 119/4 (1501-1506) CODEN: JOIMA
LANGUAGES: ENGLISH

16/3/43 (Item 18 from file: 73)
DIALOG(R)File 73:EMBASE
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889865 EMBASE No: 78056296
Suppression of acute and chronic experimental allergic encephalomyelitis in strain 13 guinea pigs. A clinical and pathological study
Raine C.S.; Snyder D.H.; Stone S.H.; Bornstein M.B.
Dept. Pathol., Saul R. Korey Dept. Neurol., Albert Einstein Coll. Med., The Bronx, N.Y. 10461 USA
J.NEUROL.SCI. (AMST.) (NETHERLANDS) , 1977, 31/3 (355-367) CODEN: JNSCA
LANGUAGES: ENGLISH

16/3/44 (Item 19 from file: 73)

DIALOG(R)File 73:EMBASE
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748115   EMBASE No: 77128622
Protection against experimental allergic encephalomyelitis with peptides derived from myelin basic protein: presence of intact encephalitogenic site is essential
Driscoll B.F.; Kies M.W.; Alvord E.C. Jr.
Sect. Myelin Chem., Lab. Cerebr. Metab., Nat. Inst. Ment. Hlth, Bethesda, Md. 20014 USA
J.IMMUNOL. (USA) , 1976, 117/1 (110-114) CODEN: JOIMA
LANGUAGES: ENGLISH

16/3/45   (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE
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644075   EMBASE No: 77021152
Experimental allergic encephalomyelitis inducing activity of synthetic polyadenylic and polyuridylic homopolymers and complexes in guinea pigs
Paterson P.Y.
Samuel J. Sackett Res. Lab., Dept. Med., Northwest. Univ. McGaw Med. Cent., Chicago, Ill. 60611 USA
CELL.IMMUNOL. (USA) , 1976, 21/1 (48-55) CODEN: CLIMB
LANGUAGES: ENGLISH

16/3/46   (Item 1 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01646642   SUPPLIER NUMBER: 18732757   (USE FORMAT 7 OR 9 FOR FULL TEXT)
The hsp60 peptide p277 arrests the autoimmune diabetes induced by the toxin streptozotocin.
Elias, Dana; Cohen, Irun R.
Diabetes, v45, n9, p1168(5)
Sep, 1996
PUBLICATION FORMAT: Magazine/Journal   ISSN: 0012-1797 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 3933   LINE COUNT: 00307

16/3/47   (Item 2 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01487423   SUPPLIER NUMBER: 15673896   (USE FORMAT 7 OR 9 FOR FULL TEXT)
Detection of borreliacidal antibodies by flow cytometry: an accurate, highly specific serodiagnostic test for Lyme disease.
Callister, Steven M.; Schell, Ronald F.; Lim, Lony C.L.; Jobe, Dean A.; Case, Kay L.; Bryant, Gary L.; Molling, Paul E.
Archives of Internal Medicine, v154, n14, p1625(8)
July 25, 1994
PUBLICATION FORMAT: Magazine/Journal   ISSN: 0003-9926 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 5419   LINE COUNT: 00472

16/3/48 (Item 3 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01373478 SUPPLIER NUMBER: 13036941 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Amelioration of autoimmune encephalomyelitis by myelin basic protein synthetic peptide-induced anergy.
Gaur, Amitabh; Wiers, Brook; Liu, Angela; Rothbard, Jonathan; Fathman, C. Garrison
Science, v258, n5087, p1491(4)
Nov 27, 1992
PUBLICATION FORMAT: Magazine/Journal ISSN: 0036-8075 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Academic
WORD COUNT: 1722 LINE COUNT: 00161

16/3/49 (Item 4 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
(c) 1997 Info Access Co. All rts. reserv.

01295278 SUPPLIER NUMBER: 10591462 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Lyme disease: clinical features, classification, and epidemiology in the upper midwest.
Agger, William; Case, Kay L.; Bryant, Gary L.; Callister, Steven M.
Medicine, v70, n2, p83(8)
March, 1991
PUBLICATION FORMAT: Magazine/Journal ISSN: 0025-7974 LANGUAGE: English
RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 4003 LINE COUNT: 00438

16/3/50 (Item 5 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01194382 SUPPLIER NUMBER: 08263509 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Product information section. (Clinical Laboratory Reference 1989) (buyers guide)
Medical Laboratory Observer, v21, n13, p16(90)
Annual, 1989
DOCUMENT TYPE: buyers guide PUBLICATION FORMAT: Magazine/Journal ISSN: 0580-7247 LANGUAGE: English RECORD TYPE: Fulltext TARGET AUDIENCE: Academic; Professional
WORD COUNT: 57949 LINE COUNT: 05915

16/3/51 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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03641460 79018460
Autoimmunity in multiple slcerosis: do we have an experimental model?
Kies MW
Adv Exp Med Biol (UNITED STATES) 1978, 100 p277-88, ISSN 0065-2598
Journal Code: 2LU
Languages: ENGLISH
Document type: JOURNAL ARTICLE

16/3/52 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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02805241 75212241
Immunologic activity of myelin basic protein in strain 2 and strain 13 guinea pigs.
Kies MW; Driscoll BF; Lisak RP; Alvord EC Jr
J Immunol (UNITED STATES) Jul 1975, 115 (1) p75-9, ISSN 0022-1767
Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

16/3/53 (Item 1 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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12009966 Genuine Article#: KD885 No. References: 60
Title: INHIBITION OF CHRONIC RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN THE BIOZZI AB/H MOUSE
Author(s): ONEILL JK; BAKER D; TURK JL
Corporate Source: ROYAL COLL SURG ENGLAND,DEPT PATHOL,35-43 LINCOLNS INN FIELDS/LONDON WC2A 3PN//ENGLAND/
Journal: JOURNAL OF NEUROIMMUNOLOGY, 1992, V41, N2 (DEC), P177-187
ISSN: 0165-5728
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

16/3/54 (Item 2 from file: 434)
DIALOG(R)File 434:Scisearch(R) Cited Ref Sci
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03785914 Genuine Article#: LF846 No. References: 0
Title: TRANSFER OF ALLERGIC ENCEPHALOMYELITIS (EAE) WITH CELLS FROM DONORS SENSITIZED WITH MYELIN BASIC-PROTEIN (BP) IN IFA
Author(s): NAMIKAWA T; RICHERT JR; DRISCOLL BF; KIES MW; ALVORD EC
Corporate Source: NIMH/BETHESDA//MD/20205; UNIV WASHINGTON,SCH MED/SEATTLE//WA/98195
Journal: FEDERATION PROCEEDINGS, 1981, V40, N3, P1028
Language: ENGLISH Document Type: MEETING ABSTRACT
?t s16/9/48,11,16,29,13,3,5,6,9,10

16/9/48 (Item 3 from file: 149)
DIALOG(R)File 149:IAC(SM)Health&Wellness DB(SM)
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01373478 SUPPLIER NUMBER: 13036941 (THIS IS THE FULL TEXT)
Amelioration of autoimmune encephalomyelitis by myelin basic protein synthetic peptide-induced anergy.
Gaur, Amitabh; Wiers, Brook; Liu, Angela; Rothbard, Jonathan; Fathman, C. Garrison
Science, v258, n5087, p1491(4)
Nov 27, 1992
PUBLICATION FORMAT: Magazine/Journal ISSN: 0036-8075 LANGUAGE: English

PE: Fulltext; Abstract TARGET AUDIENCE: Academic
OUNT: 1722 LINE COUNT: 00161

AUTHOR ABSTRACT: Experimental autoimmune encephalomyelitis (EAE), a demyelinating disease of the central nervous system that can be induced in susceptible strains of mice by immunization with myelin basic protein (MBP) or its immunodominant T cell determinants, serves as a model of human multiple sclerosis. Tolerance to MBP in adult mice was induced by intraperitoneal injection of synthetic peptides of immunodominant determinants of MBP and prevented MBP-induced EAE. Furthermore, tolerance-inducing regimens of peptides administered to mice after the disease had begun (10 days after induction with MBP) blocked the progression and decreased the severity of EAE. Peptide-induced tolerance resulted from the induction of anergy in proliferative, antigen-specific T cells.

TEXT:

Over the past decade, it has become apparent that synthetic peptides corresponding to the major immunodominant T cell determinants of native protein antigens can induce unresponsiveness both to themselves and to the native protein antigen in neonatal and adult mice [1-4]. The use of peptide-specific tolerance as a means to treat human autoimmune disease is a consequence of these studies. Murine EAE is a model of human multiple sclerosis (MS) [5] and is caused by an immune response to MBP. We have now induced tolerance to synthetic peptides corresponding to the major immunodominant determinants of MBP (peptides Ac 1-11 and 35-47) or to intact MBP by intraperitoneal injection of an emulsion of the peptide or protein in incomplete Freund's adjuvant (IFA), as has been described for tolerance induction to other proteins or peptides [3]. Two weeks after administration of tolerogen, mice were injected subcutaneously at the base of the tail with the same peptide antigen or the intact protein emulsified in complete Freund's adjuvant (CFA), the usual route of immunization. T cell proliferative assays performed on regional draining lymph node cells 10 days later revealed that the mice had been made tolerant to the peptide or protein administered as tolerogen. Both peptides Ac 1-11 and 35-47 induced tolerance to recall challenge by themselves in PL/J mice (Fig. 1A) [6].

In a separate experiment, PL/J mice were injected intraperitoneally with Ac 1-11, 35-47, intact MBP, or a mixture of the two synthetic peptides in IFA. Control mice were simply given IFA or irrelevant peptides intraperitoneally at the same time that tolerogen was administered to the experimental groups. Two weeks later, all mice were challenged with MBP (Fig. 1B). MBP was a strong tolerogen, diminishing the T cell proliferative response of regional draining lymph node cells after challenge with MBP. The mixture of the two major immunodominant determinants was almost as effective as intact MBP in inducing tolerance to a subsequent injection of MBP. The relative extent of tolerance induced by the single peptides (35-47 was less effective than Ac 1-11) corresponded to the hierarchy of immunodominance of these peptides, as assayed after priming of PL/J mice with intact MBP (Fig. 1C). In MBP peptide responses, irrelevant peptide was indistinguishable from IFA as a control [6].

We next investigated whether peptide-induced tolerance might have an impact on disease. Groups of (PL/J x SJL)[F.sub.1] mice were injected intraperitoneally with Ac 1-11, 35-37, a mixture of the two peptides, or IFA as a control 15 days before an encephalitogenic challenge with MBP [4, 7]. Intraperitoneal injection with the weakly tolerogenic (Fig. 1B) and weakly immunogenic (Fig. 1C) peptide 35-47 resulted in a modest decrease in mean clinical score and a relapsing disease (Fig. 2). The severity of EAE

[illegible] -47. The more immunodominant determinant Ac 1-11 [illegible] ent in ameliorating disease, but, as with tolerance [illegible], the mixture of the two peptides was most efficient in preventing [illegible] se (Fig. 2). The efficiency of the mixture of peptides in the prevention of EAE was better demonstrated in the comparison of mean maximum severity (MMS) scores; MMS is the mean of the highest clinical score of each animal that became sick in the group. The MMS score for the tolerance-inducing injection of the mixture of peptides was 0.52 as compared with the MMS score of 1.05 for the Ac 1-11 regimen and 3.15 for the 35-47 regimen. Control animals who were not injected with peptide had an MMS score of 3.65.

In addition to reducing the mean clinical score, the peptide mixture administered in a tolerance-inducing regimen reduced the incidence of disease in another group of (PL/J x SJL)[F.sub.1] mice (Fig. 3). Whereas 100% of control animals, who received IFA alone 15 days before encephalitogenic challenge with MBP, had developed severe and relapsing EAE by 14 days after challenge, only four of the ten mice that had been exposed to the peptide mixture showed any disease symptoms, and they quickly recovered.

Although prevention of disease in adult animals by exposure to the MBP peptide antigens was effective and suggested an approach for the prevention of autoimmune disease in humans, the development of immunotherapeutic approaches that target individuals with clinical disease is also desired. Therefore, we subjected 13 (PL/J x SJL)[F.sub.1] mice to the disease-provoking regimen of MBP [4, 7]. When this group of mice showed the first clinical signs of overt disease (day 10, when one of thirteen had a clinical score of 1, indicative of a weak tail), seven of the mice were injected intraperitoneally with the MBP peptide mixture in IFA. The remaining six mice, one of which was the animal showing the signs of disease, received no additional treatment. Only one of the seven mice that received the peptide mixture developed disease (Fig. 4). In contrast, all six of the control mice developed severe EAE (three died within 30 days of disease induction; all were dead by day 40). No disease relapse was apparent in the ensuing 90 days of observation in the treated group of mice.

Finally, we investigated the mechanism that underlies this disease treatment model. Regional draining lymph node cells were isolated 24 hours after intraperitoneal injection of the MBP peptide mixture in IFA, which was administered 10 days after primary immunization with MBP in CFA. T cell proliferative responses to MBP were diminished in lymph node cells from treated mice as compared with controls (Fig. 5). In the presence of recombinant interleukin-2 (IL-2), the antigen-specific proliferative responses of lymph node cells from the treated mice increased to amounts comparable to controls. These data support the hypothesis that the intraperitoneal administration of MBP peptides in IFA renders lymph node T cells anergic.

EAE in mice is a well-studied model of autoimmune disease in animals [4, 5, 7-11]. The immunogenetics of susceptiblity are well characterized. MBP has been analyzed for pathogenic and immunodominant T cell determinants, and at least three different regions in MBP have been identified as disease-inducing determinants in susceptible (H-[2.sup.u] and H-[2.sup.s]) strains of mice [12]. Analysis of the T cell response to these determinants in susceptible strains of mice revealed a limited use of T cell receptor (TCR) [V.sub.[unkeyable]] chain by responding T cells [13]. These data formed the basis for a disease prevention and disease therapy strategy in which researchers used monoclonal antibodies to TCR [V.sub.[unkeyable]]8.2 to eliminate cells capable of responding to peptide Ac 1-11 [14, 15]. It was possible both to prevent and to treat disease by

the removal of those T cells capable of responding to the disease-provoking encephalitogenic determinant. The success of such treatment was, however, not complete. In general, the incidence, but not the severity, of disease was diminished [16]. The enthusiasm that greeted TCR-specific immunotherapy, either by the use of monoclonal antibodies in mice [14-16] or by TCR [V.sub.[unkeyable]] peptide vaccination in rats [17, 18], has been somewhat tempered by the demonstration of multiple TCR use in response to MBP determinants in patients with MS [19-21].

Previous studies suggested that the use of peptides to treat EAE might be successful. Attempts at preventing EAE that used poorly defined antigen preparations yielded mixed results [22]. Neonatally induced tolerance to Ac 1-11 successfully prevented disease in adult mice when they were challenged with Ac 1-11 [4]. However, such neonatally tolerant mice developed severe EAE when challenged with MBP. Synthetic peptide analogs of Ac 1-11 with selective amino acid substitutions have been shown to be effective in both the prevention and the treatment of peptide-induced disease [7, 23). Such peptide analogs might be antagonists for the specific TCR, as suggested by a study on the mechanism of analog effects [24]. None of these experiments, however, successfully blocked disease induced by MBP.

The development of antigen-specific tolerance as a preventative or curative therapy may finally yield specificity of treatment for autoimmune diseases. Our data support the concept that dominance in immune response induction potential of synthetic peptides of MBP is directly correlated with their tolerance induction potential. Further, we showed that tolerance induction with peptides before challenge with MBP blocked disease induction in a similar hierarchy. Finally, a mixture of the immunodominant determinants of MBP (Ac 1-11 and 35-47) delivered in a tolerogenic manner successfully treated ongoing disease by inducing anergy in the antigen-specific T cells.

REFERENCES AND NOTES

1. A. Oki and E. Sercarz, J. Exp. Med. 161, 897 (1985).

2. G. Gammon et al., Nature 319, 413 (1986).

3. F. Ria, B. M. C. Chan, M. T. Scherer, J. A. Smith, M. L. Gefter, ibid. 343, 381 (1990).

4. J. P. Clayton et al., J. Exp. Med. 169, 1681 (1989).

5. H. M. Wisniewski and A. B. Keith, Ann. Neurol. 1, 144 (1977).

6. We confirmed antigen specificity of the unresponsiveness by treating mice intraperitoneally with a control peptides [amino acids 110 to 121 of sperm whale myoglobin (SWM)] and later immunizing with MBP peptide. Responses to 25 [unkeyable]M Ac 1-11 were similar in both the IFA-treated and SWM (110-121)-treated mice. The radioactivities were 13,576 [+ or -] 2,455 cpm (mean [+ or -] SEM; n = 3) and 14,502 [+ or -] 979 cpm for the two groups, respectively. Similarly, MBP peptides given in a tolerogenic manner did not affect the response after immunization of (PL/J x SJL)[F.sub.1] mice with 100 [unkeyable]g of an immunogenic peptide [amino acids 39 to 61 from the variable region of the [unkeyable] ([V.sub.[unkeyable]]8.2) chain of the T cell receptor]; the results were 74,193 [+ or -] 4,179 cpm for the IFA-treated group and 72,787 [+ or -] 7,506 cpm for the MBP peptide-treated group in response to challenge with 5 [unkeyable]M 39-61 TCR peptide.

7. D. E. Smilek et al., Proc. Natl. Acad. Sci. U.S.A. 88, 9633 (1991).

8. R. B. Fritz, C. H. Jen-Chou, D. E. McFarlin, J. Immunol. 130, 191 (1983); S. S. Zamvil et al., Nature 324, 258 (1986).

9. D. H. Kono et al., J. Exp. Med. 168, 213 (1988).

10. S. W. Brostoff and D. W. Mason, J. Immunol. 133, 1938 (1984).

11. M. K. Waldor et al., Science 227, 415 (1985).

12. S. S. Zamvil et al., J. Exp. Med. 168, 1181 (1988).

13. S. S. Zamvil et al., ibid. 167, 1586 (1988).
14. H. Acha-Orbea et al., Cell 54, 263 (1988).
15. J. L. Urban et al., ibid., p. 577.
16. D. M. Zaller, G. Osman, O. Kanagawa, L. Hood, J. Exp. Med. 171, 1943 (1990).
17. A. A. Vandenbark, G. Hashim, H. Offner, Nature 341, 541 (1989).
18. M. D. Howell et al., Science 246, 668 (1989).
19. D. A. Hafler et al., J. Exp. Med. 167, 1313 (1988).
20. R. Martin et al., ibid. 173, 19 (1991).
21. R. Martin et al., J. Immunol. 148, 1359 (1992).
22. E. C. Alvord, Jr., C. Shaw, S. Hruby, M. W. Kies, Ann. N.Y. Acad. Sci. 1220, 333 (1965); B. Campbell, P. J. Vogel, E. Fisher, R. Lorenz, Arch. Neurol. 29, 10 (1973); B. F. Driscoll, M. W. Kies, E. C. Alvord, Jr., J. Immunol. 117, 110 (1976); G. A. Hashim and F. J. Schilling, Arch. Biochem. Biophys. 156, 287 (1973); E. H. Eylan et al., Nature 236, 74 (1972); B. F. Driscoll, M. W. Kies, E. C. Alvord, Jr., J. Immunol. 112, 392 (1974).
23. D. C. Wraith, D. E. Smilek, D. J. Mitchell, L. Steinman, H. O. McDevitt, Cell 59, 247 (1989).
24. T. DeMagistris et al., ibid. 68, 625 (1992).
25. We thank H. Y. Tse for providing guinea pig MBP, L. Steinman and H. O. McDevitt for critical review of the manuscript, and R. Kizer and K. Sturgis for preparation of the manuscript. Supported by the Multiple Sclerosis Society and NIH grant Al 27989. A. G. was a fellow of the American Diabetes Association.
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SPECIAL FEATURES: illustration; graph
DESCRIPTORS: Immunological tolerance--Physiological aspects; Multiple sclerosis--Models
FILE SEGMENT: MI File 47

16/9/11 (Item 11 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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4502048 BIOSIS Number: 78075871

PARTICIPATION OF ENCEPHALITOGEN IN INCOMPLETE FREUNDS ADJUVANT IN THE INDUCTION OF EXPERIMENTAL ALLERGIC ENCEPHALO MYELITIS IN HARTLEY GUINEA-PIGS

LEBAR R; VINCENT C
U 23 INSERM, HOPITAL ST-ANTOINE, 184, RUE DE FG ST-ANTOINE, 75571 PARIS CEDEX 12, FR.
J NEUROIMMUNOL 6 (3). 1984. 187-196. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH
The addition of complete Freund's adjuvant (CFA) to encephalitogen is required for the induction of experimental allergic encephalomyelitis (EAE). Administration of encephalitogen in incomplete Freund's adjuvant (IFA) protects the animal from the development of EAE. Injection of homologous CNS tissue or myelin basic protein (BP) in IFA, before challenge with CNS tissue in CFA, accelerated the onset of the disease in Hartley guinea pigs. It also appeared to protect the animals, because 22% of the group did not develop EAE at all, and in those which did, the disease was not as lethal as in controls. To produce this accelerated form of EAE with

ncephalitogen in IFA required a time interval shorter than 9 days between the 1st injection and challenge and that the 1st injection and the challenge be done in the same site, which could be hind or front foot pads but not the nuchal area. Priming by encephalitogen in IFA occurred when this 2-step induction procedure was used. The experimental conditions may have bypassed suppressive mechanisms.

Descriptors/Keywords: COMPLETE FREUNDS ADJUVANT MYELIN BASIC PROTEIN

Concept Codes:

- *20506 Nervous System-Pathology
- *34502 Immunology and Immunochemistry-General; Methods
- *34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
- *35500 Allergy
- 10060 Biochemical Studies-General
- 10064 Biochemical Studies-Proteins, Peptides and Amino Acids
- 12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
- 31000 Physiology and Biochemistry of Bacteria
- 34504 Immunology and Immunochemistry-Bacterial, Viral and Fungal

Biosystematic Codes:

- 05822 Mycobacteriaceae (1979-)
- 86300 Caviidae

Super Taxa:

Microorganisms; Bacteria; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

16/9/16 (Item 16 from file: 5)

DIALOG(R)File 5:BIOSIS PREVIEWS(R)

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3724878 BIOSIS Number: 74024741

TRANSFER OF ALLERGIC ENCEPHALO MYELITIS WITH SPLEEN CELLS FROM DONORS SENSITIZED WITH MYELIN BASIC PROTEIN IN INCOMPLETE FREUNDS ADJUVANT

NAMIKAWA T; RICHERT J R; DRISCOLL B F; KIES M W; ALVORD E C JR
SECT. MYELIN CHEM., LAB. CEREBRAL METAB., NATL. INST. MENT. HEALTH, BETHESDA, MD. 20205.

J IMMUNOL 128 (2). 1982. 932-934. CODEN: JOIMA
Full Journal Title: Journal of Immunology
Language: ENGLISH

Myelin basic protein (BP) emulsified in incomplete Freund's adjuvant (BP/IFA) is relatively nonencephalitogenic in Lewis rats. Repeated injections of BP/IFA prevent subsequent induction of experimental allergic encephalomyelitis (EAE) by BP emulsified in complete Freund's adjuvant (BP/CFA). Spleen cells from rats injected repeatedly with BP/IFA transfer EAE after they are cultured with BP almost as effectively as BP/CFA spleen cells. Unlike the latter, BP/IFA spleen cells do not proliferate in response to BP in culture. BP/IFA spleen cells are unable to transer EAE after culture with concanavalin A (Con A), in contrast to BP/CFA spleen cells. Both populations of spleen cells undergo a strong proliferative response to Con A in culture. For BP/IFA cells, at least, a proliferative response to BP in vitro is not a prerequisite for enhanced transfer of EAE in Lewis rats.

Descriptors/Keywords: LEWIS RATS COMPLETE FREUNDS ADJUVANT CONCANAVALIN A

Concept Codes:

- *15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
- *15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System

*20506 Nervous System-Pathology
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
02506 Cytology and Cytochemistry-Animal
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
20501 Nervous System-General; Methods
22008 Pharmacology-Blood and Hematopoietic Agents
22018 Pharmacology-Immunological Processes and Allergy
31000 Physiology and Biochemistry of Bacteria
34502 Immunology and Immunochemistry-General; Methods
35500 Allergy
51522 Plant Physiology, Biochemistry and Biophysics-Chemical Constituents
54000 Pharmacognosy and Pharmaceutical Botany

Biosystematic Codes:
05822 Mycobacteriaceae (1979-)
26260 Leguminosae
86375 Muridae

Super Taxa:
Microorganisms; Bacteria; Plants; Vascular Plants; Spermatophytes; Angiosperms; Dicots; Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

16/9/29 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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5630763 EMBASE No: 84126429
Participation of encephalitogen in incomplete Freund's adjuvant in the induction of experimental allergic encephalomyelitis in Hartley guinea pigs
Lebar R.; Vincent C.
Centre d'Immuno-Pathologie et d'Immunologie Experimentale, INSERM (U 23), CNRS (LA 289), Hopital St.-Antoine, 75012 Paris FRANCE
J. NEUROIMMUNOL. (NETHERLANDS) , 1984, 6/3 (187-196) CODEN: JNRID
LANGUAGES: ENGLISH
The addition of complete Freund's adjuvant (CFA) to encephalitogen is required for the induction of experimental allergic encephalomyelitis (EAE). On the other hand, administration of encephalitogen in incomplete Freund's adjuvant (IFA) protects the animal from the development of EAE. It is shown in this work that injection of homologous central nervous system (CNS) tissue or myelin basic protein (BP) in IFA, before challenge with CNS tissue in CFA, accelerated the onset of the disease in Hartley guinea pigs. It also appeared to protect the animals, however, because 22% of the group did not develop EAE at all, and in those which did, the disease was not as lethal as in controls. To produce this accelerated form of EAE with encephalitogen in IFA required (1) a time interval shorter than 9 days between the first injection and challenge and (2) that the first injection and the challenge be done in the same site, which could be hind or front foot pads but not the nuchal area. The results indicated that 'priming' by encephalitogen in IFA occurred when this two-step induction procedure was used. The experimental conditions may have bypassed suppressive mechanisms.

EMTAGS:
Central nervous system (0912); Immunological procedures (0102); Nonhuman (0777); Etiology (0135); Iatrogenic disease (0300); Guinea pig (0717);

Immunological factors (0136); Animal experiment (0112); Animal tissue, cells or cell components (0105)
DESCRIPTORS:
*encephalitogenic agent (0071743); *freund adjuvant (0018490); *allergic encephalomyelitis (0001574); *central nervous system (0008370)

IDENTIFIERS: guinea pig
SECTION HEADINGS:
02606000000 IMMUNOLOGY AND SEROLOGY/ HYPERSENSITIVITY MEDIATED BY ANTIBODIES
02602000000 /ANTIGENS
02604030000 /ANTIGEN-ANTIBODY REACTIONS AND COMPLEXES/ Antigen-antibody reactions
02609010000 /IMMUNOCOMPETENCE/ Humoral immunity
00822010000 NEUROLOGY AND NEUROSURGERY/ DEMYELINATING DISEASES/ Experimental aspects
00840010000 /NEUROIMMUNOLOGY/ Experimental aspects
02907120000 CLINICAL BIOCHEMISTRY/ BODY CONSTITUENTS/ Nervous tissue
02905000000 /IMMUNOCHEMISTRY

16/9/13 (Item 13 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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3988361 BIOSIS Number: 75035720
CHRONIC RELAPSING EXPERIMENTAL AUTO IMMUNE ENCEPHALO MYELITIS TREATMENT WITH COMBINATION OF MYELIN COMPONENTS PROMOTES CLINICAL AND STRUCTURAL RECOVERY
TRAUGOTT U; STONE S H; RAINE C S
DEPARTMENT OF PATHOLOGY, K-433, ALBERT EINSTEIN COLLEGE OF MEDICINE, 1300 MORRIS PARK AVENUE, BRONX, N. Y. 10461, U.S.A.
J NEUROL SCI 56 (1). 1982. 65-74. CODEN: JNSCA
Full Journal Title: Journal of the Neurological Sciences
Language: ENGLISH
Preliminary results are presented on the treatment of strain 13 guinea pigs with chronic relapsing experimental autoimmune (allergic) encephalomyelitis (EAE) induced by a single sensitization with whole spinal cord. Animals were treated at different stages of the disease with injections containing either myelin basic protein (MBP) alone in incomplete Freund's adjuvant (IFA), or MBP in combination with a lipid hapten of myelin, galactocerebroside (GC) in IFA. The rationale for this treatment stemmed from previous work which suggested that MBP was responsible for T cell sensitization in EAE and that GC was important in producing demyelinating antibodies. Both myelin components were needed in the induction of disease. Although treatment with MBP alone caused some initial stabilization of the disease process, subsequent relapses occurred in all animals. In animals given MBP and GC together, either early or late in the course of the disease, marked clinical improvement was noted with little or no development of relapses over an observation period of > 1 yr posttreatment. Evidence of extensive remyelination and oligodendroglial proliferation in CNS lesions was found in MBP-GC-treated animals suggesting that this therapy might be beneficial for CNS repair and relevant to multiple sclerosis.
Descriptors/Keywords: STRAIN 13 GUINEA-PIG MYELIN BASIC PROTEIN INCOMPLETE FREUNDS ADJUVANT GALACTO CEREBROSIDE T CELL RE MYELINATION OLIGODENDRO GLIAL PROLIFERATION MULTIPLE SCLEROSIS MODEL
Concept Codes:

*02506 Cytology and Cytochemistry-Animal
*12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
*13004 Metabolism-Carbohydrates
*13006 Metabolism-Lipids
*13012 Metabolism-Proteins, Peptides and Amino Acids
*13020 Metabolism-Metabolic Disorders
*20506 Nervous System-Pathology
*22018 Pharmacology-Immunological Processes and Allergy
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
*35500 Allergy
10060 Biochemical Studies-General
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10066 Biochemical Studies-Lipids
10068 Biochemical Studies-Carbohydrates
12512 Pathology, General and Miscellaneous-Therapy (1971-)
17016 Endocrine System-Thymus
20504 Nervous System-Physiology and Biochemistry
22100 Routes of Immunization, Infection and Therapy
34502 Immunology and Immunochemistry-General; Methods

Biosystematic Codes:
86000 Erinaceidae

Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Insectivores

16/9/3 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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12052376 BIOSIS Number: 98652376

Protracted, relapsing and demyelinating experimental autoimmune encephalomyelitis in DA rats immunized with syngeneic spinal cord and incomplete Freund's adjuvant

Lorentzen J C; Issazadeh S; Storch M; Mustafa M I; Lassman H; Linington C ; Klareskog L; Olsson T
Dep. Rheumatol., Karolinska Hospital, Karolinska Inst., S-17176 Stockholm, Sweden

Journal of Neuroimmunology 63 (2). 1995. 193-205.
Full Journal Title: Journal of Neuroimmunology
ISSN: 0165-5728
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 005 Ref. 068121

Experimental autoimmune encephalomyelitis (EAE) is a model for multiple sclerosis (MS). However, MS is a chronic, relapsing and demyelinating disease, whereas EAE in rats is typically a brief and monophasic disorder showing little demyelination. We demonstrate here that DA rats develop severe, protracted and relapsing EAE (SPR-EAE) after a subcutaneous immunization at the tail base with syngeneic spinal cord and incomplete Freund's adjuvant (IFA). The neurological deficits were accompanied by demyelinating inflammatory lesions in the spinal cord, with infiltrating T lymphocytes and perivascular deposition of immunoglobulins and complement. The induction of SPR-EAE was associated with humoral autoreactivity to myelin oligodendrocyte glycoprotein (MOG) and cellular autoreactivity to the rat myelin basic protein (MBP) peptides 69-87 and 87-101. These two peptides, as well as whole rat MBP, were encephalitogenic. In conclusion,

we believe that the presently described demyelinating SPR-EAE represents a useful model for MS.

Descriptors/Keywords: RESEARCH ARTICLE; IMMUNOGLOBULIN; COMPLEMENT SYSTEM; MYELIN OLIGODENDROCYTE GLYCOPROTEIN; MYELIN BASIC PROTEIN; T LYMPHOCYTE; INFLAMMATION; MULTIPLE SCLEROSIS

Concept Codes:

*02506 Cytology and Cytochemistry-Animal
*12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
*13004 Metabolism-Carbohydrates
*13006 Metabolism-Lipids
*13012 Metabolism-Proteins, Peptides and Amino Acids
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*20506 Nervous System-Pathology
*22501 Toxicology-General; Methods and Experimental
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
10060 Biochemical Studies-General
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10066 Biochemical Studies-Lipids
10068 Biochemical Studies-Carbohydrates

Biosystematic Codes:

86375 Muridae

Super Taxa:

Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

16/9/5 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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9138450 BIOSIS Number: 93123450

STUDIES OF V-BETA-8 T CELL RECEPTOR PEPTIDE TREATMENT IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

STEVENS D B; KARPUS W J; GOULD K E; SWANBORG R H
DEP. IMMUNOLOGY MICROBIOLOGY, WAYNE STATE UNIV. SCH. MED., 540 EAST CANFIELD AVENUE, DETROIT, MICH. 48201, USA.

J NEUROIMMUNOL 37 (1-2). 1992. 123-129. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH

Lewis rats immunized with T cell receptor (TCR) variable region peptide V.beta.8 in complete Freund's adjuvant (CFA) were protected against experimental autoimmune encephalomyelitis (EAE) induced with myelin basic protein in CFA, although variable protection was also observed in rats injected with control peptide in CFA, or CFA alone. However, this adjuvant-mediated protection could be avoided by immunizing with TCR peptide in incomplete adjuvant (IFA). Clinical, but not histologic EAE was suppressed in rats given V.beta.8 peptide in IFA, whereas control animals injected with V.beta.14 peptide in IFA, or IFA alone developed severe clinical EAE. Anti-V.beta.8 antibodies were present in the sera of all V.beta.8-treated rats. These findings lend support to the hypothesis that autoimmune disease can be suppressed by inducing an immune response against the TCR-idiotope of autoreactive T cells.

Descriptors/Keywords: RAT AUTOIMMUNE DISEASE SUPPRESSION MYELIN BASIC PROTEIN AUTOREACTIVE T CELL IMMUNE RESPONSE

Concept Codes:
  *02506   Cytology and Cytochemistry-Animal
  *10508   Biophysics-Membrane Phenomena
  *12508   Pathology, General and Miscellaneous-Inflammation and
           Inflammatory Disease
  *13012   Metabolism-Proteins, Peptides and Amino Acids
  *15008   Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and
           Reticuloendothelial System
  *20506   Nervous System-Pathology
  *34508   Immunology and Immunochemistry-Immunopathology, Tissue
           Immunology
   10064   Biochemical Studies-Proteins, Peptides and Amino Acids
Biosystematic Codes:
   86375   Muridae
Super Taxa:
   Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman
    Mammals; Rodents

16/9/6   (Item 6 from file: 5)
DIALOG(R)File   5:BIOSIS PREVIEWS(R)
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8083917   BIOSIS Number: 91004917
  ABROGATION OF INDUCED RESISTANCE TO EXPERIMENTAL ALLERGIC
ENCEPHALOMYELITIS IN GUINEA-PIGS BY HOST-VERSUS-GRAFT REACTION
  KOZOVSKA M; STAYKOVA M; GORANOV I
  INST. CELL BIOL. MORPHOL., ACAD. G. BONTCHEV STR. 25 1113 SOFIA,
BULGARIA.
  J NEUROIMMUNOL 29 (1-3). 1990. 157-164.   CODEN: JNRID
  Full Journal Title: Journal of Neuroimmunology
  Language: ENGLISH
  Experimental allergic encephalomyelitis (EAE) effector cells known to exist in guinea pigs with myelin basic protein-incomplete Freund's adjuvant (MBP-IFA)-induced resistance to EAE could be activated in vivo by means of allogeneic conformation (local host-versus-graft reaction (HVGR)). The abrogation of the resistance was observed only when HVGR was combined with encephalitogenic challenge (myelin basic protein-complete Freund's adjuvant (MBP-CFA)) in a certain order and at certain time intervals. The injection of 20 .times. 107 .gamma.-irradiated allogeneic lymphoid cells 7 or 4 days prior to or along with MBP-CFA treatment resulted in development of EAE with delayed onset and protracted course. The effect was most prominent when HVGR was induced on day -4. Histological examination revealed inflammatory lymphoid cell infiltrations in spinal cord. Serum level of total and anaphylactic anti-MBP antibodies correlated with the clinical picture.
Descriptors/Keywords: MYELIN BASIC PROTEIN COMPLETE FREUND'S ADJUVANT
  INFLAMMATORY LYMPHOID CELL INFILTRATION ANAPHYLAXIS
Concept Codes:
  *02506   Cytology and Cytochemistry-Animal
  *03506   Genetics and Cytogenetics-Animal
  *12508   Pathology, General and Miscellaneous-Inflammation and
           Inflammatory Disease
  *15004   Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
  *15008   Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and
           Reticuloendothelial System
  *20506   Nervous System-Pathology
  *34508   Immunology and Immunochemistry-Immunopathology, Tissue

Immunology
*35500 Allergy
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
20504 Nervous System-Physiology and Biochemistry
Biosystematic Codes:
86300 Caviidae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

16/9/9 (Item 9 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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5379463 BIOSIS Number: 82024266
THE ROLE OF MYELIN LIPIDS IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS III. TRANSFER OF SUPPRESSION FROM GUINEA-PIGS RECOVERING FROM EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS INDUCED BY MYELIN BASIC PROTEIN-GALACTOCEREBROSIDE COMPLEXES
HOSEIN Z Z; GILBERT J J; STREJAN G H
DEP. OF IMMUNOL, KAROLINSKA INSTITUTET, STOCKHOLM, SWEDEN.
CELL IMMUNOL 99 (1). 1986. 265-278. CODEN: CLIMB
Full Journal Title: Cellular Immunology
Language: ENGLISH
Juvenile strain 13 guinea pigs were immunized with myelin basic protein (MBP) combined with galactocerebrosides (MBP + GC) or with total myelin lipids without GC [MBP + (TL-GC)] in CFA. Control animals received dinitrophenylated-ovalbumin (DNP-OA) in CFA, CFA or IFA alone. The animals injected with MBP + GC showed a higher rate of recovery from the first EAE episode (83%) than those treated with MBP + (TL-GC) (50%). With the exception of the group treated with IFA alone, all animals were refractory to EAE following rechallenge with MBP in CFA 90 days after the first exposure. The in vitro proliferative response to MBP, or peripheral blood lymphocytes (PBLs) derived from guinea pigs freshly sensitized to MBP in CFA, was drastically suppressed in the presence of PBLs from animals injected with MBP + GC. Upon transfer to normal syngeneic recipients, spleen cells from MBP + GC-treated animals completely suppressed the clinical and histological manifestations of EAE following recipient challenge with MBP in CFA. Cell-free supernatants from PBLs and spleen cells of strain 13 guinea pigs treated with MBP + GC inhibited lymphocyte proliferation to MBP, of allogeneic responder cells, and spleen cell supernatants completely suppressed the induction of EAE upon transfer to allogeneic recipients. Suppression could not be transferred with cells from other treated groups. These results suggest that animals immunized with MBP + galactocerebrosides in CFA develop suppressor cells that may be in part responsible for the recovery from the first EAE episode and for protection against rechallenge with MBP in CFA. Their cell-free supernatants act in an MHC-nonrestricted fashion. These results do not rule out an additional protective mechanism since all animals exposed to CFA were refractory to rechallenge despite lack of demonstrable suppressor cell activity.
Descriptors/Keywords: MULTIPLE SCLEROSIS MODEL PERIPHERAL BLOOD LYMPHOCYTE CELL PROLIFERATION
Concept Codes:
*12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
*15004 Blood, Blood-Forming Organs and Body Fluids-Blood Cell Studies
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and

Reticuloendothelial System
*20506 Nervous System-Pathology
*25508 Developmental Biology-Embryology-Morphogenesis, General
*34508 Immunology and Immunochemistry-Immunopathology, Tissue
Immunology
*35500 Allergy
02506 Cytology and Cytochemistry-Animal
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10066 Biochemical Studies-Lipids
10068 Biochemical Studies-Carbohydrates
32600 In Vitro Studies, Cellular and Subcellular
34502 Immunology and Immunochemistry-General; Methods
Biosystematic Codes:
86300 Caviidae
Super Taxa:
Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman Mammals; Rodents

16/9/10 (Item 10 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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4816532 BIOSIS Number: 79058847
SUPPRESSION OF CHRONIC-RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS IN STRAIN-13 GUINEA-PIGS BY ADMINISTRATION OF LIPOSOME-ASSOCIATED MYELIN BASIC PROTEIN
STREJAN G H; GILBERT J J; ST LOUIS J
DEP. MICROBIOLOGY IMMUNOLOGY, UNIV. WESTERN ONT., HEALTH SCI. CENTER, LONDON, ONT., CAN.
J NEUROIMMUNOL 7 (1). 1984. 27-42. CODEN: JNRID
Full Journal Title: Journal of Neuroimmunology
Language: ENGLISH
Juveile strain-13 guinea pigs were challenged with isologous spinal cord in CFA [complete Freunds adjuvant]. After recovery from the first EAE [experimental allergic encephalomyelitis] episode the animals were treated with guinea pig MBP inserted into liposomes, with cytochrome-c-liposomes, with MBP in saline or with MBP in IFA. Guinea pigs treated with MBP-liposomes showed a striking reduction in clinical signs and in the number and intensity of relapses. They displayed virtually no demyelinating lesions, and had comparatively little parenchymal inflammation in the spinal cord. Early T rosette levels showed an inverse correlation with the severity of histological lesions in the spinal cord, but correlation with the clinical status at the time of rosette assay was less well defined.
Descriptors/Keywords: T CELL ROSETTING SPINAL CORD CYTOCHROME C LIPOSOMES
Concept Codes:
*12508 Pathology, General and Miscellaneous-Inflammation and Inflammatory Disease
*15008 Blood, Blood-Forming Organs and Body Fluids-Lymphatic Tissue and Reticuloendothelial System
*20501 Nervous System-General; Methods
*20506 Nervous System-Pathology
*34508 Immunology and Immunochemistry-Immunopathology, Tissue Immunology
01056 Microscopy Techniques-Histology and Histochemistry
02506 Cytology and Cytochemistry-Animal
10064 Biochemical Studies-Proteins, Peptides and Amino Acids
10065 Biochemical Studies-Porphyrins and Bile Pigments

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   10802   Enzymes-General and Comparative Studies; Coenzymes
   13004   Metabolism-Carbohydrates
   13006   Metabolism-Lipids
   13012   Metabolism-Proteins, Peptides and Amino Acids
   35500   Allergy
Biosystematic Codes:
   86300   Caviidae
Super Taxa:
   Animals; Chordates; Vertebrates; Nonhuman Vertebrates; Mammals; Nonhuman
    Mammals; Rodents
?ds
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Set	Items	Description
S1	0	TH2(W)RESPONSE(W)INDUCING(W)ADJUVANT
S2	1174	E1-E31
S3	129	E1-E14
S4	1303	S2 OR S3
S5	15	S4 AND TH2
S6	8	RD (unique items)
S7	23	TH2 AND AUTOIMMUN
S8	1403	TH2 AND AUTOIMMUN?
S9	120	S8 AND ADJUVANT?
S10	120	S9
S11	78	RD (unique items)
S12	78	S11 NOT S6
S13	16	S8 AND IFA
S14	9	RD (unique items)
S15	96	(MBP OR (MYELIN(W)BASIC(W)PROTEIN)) AND IFA
S16	54	RD (unique items)

2. 5,571,500, Nov. 5, 1996, Treatment of autoimmune diseases through administration by inhalation of autoantigens; David A. Hafler, et al., 424/43, 44, 45, 46; 514/2, 825, 903 [IMAGE AVAILABLE]

US PAT NO: 5,571,500 [IMAGE AVAILABLE] L1: 2 of 7

ABSTRACT:
Disclosed herein is a method for treating autoimmune diseases in mammals by administration of one or more agents selected from the group consisting of autoantigens specific for the autoimmune disease, disease-suppressive fragments and analogs of said autoantigen in aerosol form.

3. 5,571,499, Nov. 5, 1996, Treatment of autoimmune diseases by aerosol administration of autoantigens; David A. Hafler, et al., 424/43, 44, 45, 46; 514/2, 825, 903 [IMAGE AVAILABLE]

US PAT NO: 5,571,499 [IMAGE AVAILABLE] L1: 3 of 7

ABSTRACT:
Disclosed herein is a method for treating autoimmune diseases in mammals by administration of one or more agents selected from the group consisting of autoantigens specific for the autoimmune disease, disease-suppressive fragments and analogs of said autoantigen in aerosol form.